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Alcohol: its absorption into and disappearance from the blood under different conditions

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(National Health Insurance.)

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INTRODUCTION

The work described in the present Report was undertaken at the request of the Central Control Board (Liquor Traffic) by Dr. Edward Mellanby, whose services were lent, with the provision of the necessary expenses, by the Medical Research Committee. The Committee are glad to publish these results in their present form at the suggestion of the Board.

The auspices under which this investigation was begun and carried out made it natural that the experiments should be planned with special reference to practical issues. Their primary aim was to decide how far the circumstances in which a given amount of alcohol is consumed can affect the degree of intoxication produced by it. The investigation, so far as it is described in the present Report, was confined to the use of dogs as subjects, and Dr. Mellanby is careful to emphasize the difficulty of estimating or expressing the intensity of intoxication as shown by an animal in any terms which could be applied with certainty to a human being. His statements are based upon objective facts, and in the main upon the study of a variable which can be accurately estimated and quantitatively expressed. He has determined, in various circumstances, the concentration of alcohol in the blood found at known periods after giving a definite dose by the mouth. That the various factors shown to affect the results in a dog are likely to have a corresponding influence in man is a proposition that may well be granted. We learn indeed that preliminary experiments already carried out on human beings indicate that the results are strictly comparable. That measurements of the concentration of alcohol in the blood, and of the velocity with which a maximal concentration is reached, should yield information as to the degree of intoxication associated with the consumption of a beverage under this or that condition, is a reasonable assumption.

Dr. Mellanby shows that the maximal concentration in the blood, which occurs very soon after the alcohol is consumed, is, within certain limits, proportional to the amount taken. On the other hand, and because the disappearance of the alcohol from the blood is remarkably slow—an interesting and important fact illustrated in all the observations described—a given amount of spirit produces the same maximal concentration whether it be taken in one dose or in divided doses at intervals which may extend to two hours. The effect is cumulative. A definite amount of alcohol taken in a dilute form accumulates in the blood more slowly and reaches a lower maximum than when it is taken undiluted. The weaker the beverage therefore the more actual

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alcohol must be consumed in order that a definite degree of intoxication should be reached.

While this effect of dilution is well established by the experiments, it is noteworthy that the consumption of water or other fluids a few hours before a dose of alcohol is taken leads to more rapid absorption of the latter, and consequently—for a given dose—to more intense intoxication.

Food-stuffs inhibit intoxication in consequence of their action in delaying absorption from the alimentary canal. The most effective food-stuff in this respect is milk. Its specific influence in delaying absorption more than counterbalances its general effect as a fluid, and Dr. Mellanby comments upon the striking differences observed in the effects of a dose of alcohol when given two hours after the consumption of half a litre of water and after half a litre of milk respectively. In the first case a dog may become incapable of standing or walking, in the latter case it may show no sign whatever of unsteadiness.

Such points as these are mentioned here in illustration of the practical bearing of Dr. Mellanby's results. The student of metabolism will find much of interest in the facts, so well established by the experiments, that alcohol disappears from the circulation with remarkable slowness and at a rate which is independent of the concentration. Of no less interest is the evidence which suggests—though doubtless it fails to prove—that alcohol is incapable of yielding energy to the muscles.

Medical Research Committee,
15 Buckingham Street,
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ALCOHOL: ITS ABSORPTION INTO AND DISAPPEARANCE FROM THE BLOOD UNDER DIFFERENT CONDITIONS.

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CONTENTS

I. Introduction.

The experimental work described in the following pages is the result of a request by the Chairman of the Central Control Board (Liquor Traffic) to supply certain information in order that the policy of controlling the sale of liquor might be guided and assisted by the results of scientific inquiry. The request was of a comprehensive nature, and presented such problems as the effect of dilution on the intoxicating properties of alcohol, the modifying action (if any) of food-stuffs at different stages of digestion on

alcoholic intoxication, variations in the effects of beverages imbibed, and so on. It will be seen that definite answers have been supplied to some of these questions, at least so far as experimental animals (dogs) are concerned. As regards some points, the work has provided information along lines which were unexpected at the outset, and, in some cases, has presented a picture seen at a different angle from that of other workers on alcohol, with the result that new conceptions of the physiological action of this substance seem justifiable.

It is necessary to point out the limitations of work of this type. In all cases alcohol has been placed directly into the stomach of dogs and the amount in the blood estimated at different times. The results therefore only give an accurate account of the rate of absorption of alcohol from the alimentary canal and its rate of disappearance from the blood-stream. Now, although there is an unquestionable relationship between alcohol in the blood and intoxication, it is not certain that the relation between the two is close enough to allow the latter to be strictly determined from the former. This fact would not be of much importance if there were as accurate a measure of intoxication as there is of alcohol in the blood, but this is not the case. It is evident that even in the case of a man it is difficult to get a complete measure of a nervous defect like intoxication. In dogs it has been impossible under the present conditions of the work. This point will be considered in more detail later, but meantime it is clear that, although from the point of view of the Central Control Board, the answer to the questions presented should be given in terms of intoxication rather than of alcohol in the blood, it is just at this point the work fails. A further criticism, although this I consider of less importance, is that the results obtained from dogs may not apply to man.[1]

These limitations suggest that this work is to be regarded as a basis for other work rather than as offering definite solutions to the problems presented. Great differences have been observed in the amounts of alcohol in the blood under varying conditions, and, incidentally, great differences in intoxication, but it seems to me that the experiments should be extended to men, using these results as the basis. In future experiments the psychologist should apply his methods for measuring symptoms of intoxication, while, at the same time, estimations of the alcohol in the blood should be made so as to control and confirm the present work.

Finally, it may be added that the present investigation has been led a short way along many side paths, which, if followed up, promise interesting information. It is possible that further work will be undertaken to open up these new lines.

II. Experimental Procedure.

The experiments to be described have been made on four dogs which will be known throughout as brown, large black, small black,

[1] I have more recently repeated some of the experiments on man and, except that he is more susceptible to alcohol, the results so far obtained are comparable.

and white. The weights of the dogs have been approximately as follows:

Brown . .	13·0 to 14·6 kilograms.
Large black . . .	12·5 "
Small black . . .	11·35 "
White	10·0 "

Under war conditions these weights have varied from time to time.

Definite quantities of alcohol made up to varying strengths according to the nature of the experiment were placed directly into the stomach by a tube passed down the oesophagus.

In order to do this the dog was placed in a sack held firmly at the neck. As a rule there was no difficulty in this operation. When large quantities of fluid were used—in some cases 1,200 c.c. of fluid were poured into the stomach—it was essential to proceed slowly and allow the stomach to adapt itself to the large volume. Otherwise the dog would vomit large quantities. The time taken for the injection varied from 1 to 5 minutes according to the volume of fluid used. After injecting the alcohol it is essential that the dogs should be closely watched, more particularly if a strong alcoholic solution, i. e. 20 per cent. or over, be used. The irritating action of the alcohol on the mucous membrane of the stomach often causes the dog to vomit small quantities, and this deprives the experiments of any value; for, even if only 1 c.c. of alcohol is lost in this way, it makes a considerable difference to the alcohol-in-the-blood results. With dilute alcoholic solutions this danger is not so great, but in all cases it is advisable to keep the dogs quiet for about 10 minutes after the injection, and to watch them closely during the next hour. Unless the animals are very intoxicated the danger of vomiting is small after this time, but, if marked intoxication is produced, the danger of vomiting is never absent during the experiment.

In experiments of this type it is clear that so many variable factors present themselves that precautions must be taken to keep the animals in as uniform a condition as possible. The achievement of this object has been only partially successful, so that, although there may be many other points of interest in the results obtained, only those points are mentioned in which there is fair unanimity among the different dogs. It was necessary to have the stomach and small intestine in a definite condition according to the experiment, so that, except where otherwise stated, the dogs were each given 1 lb. of meat at 2 p.m. on the day prior to the experiment. When this was eaten (always a matter of minutes) the water in the kennels was also withdrawn, and no other food or water given until the experiment started, usually at 10 a.m. the following day. At the time of the experiment, therefore, the stomach and small intestines were empty except for that food, the influence of which on alcohol absorption was being tested.

The varying temperature according to the time of year must have had some effect on the development of thirst in the dogs. Except that they were not allowed to exercise after the withdrawal of water, this question of thirst, which will be seen to be of some importance as regards the rate of absorption of alcohol, has not been as well controlled as is desirable. A greater source of error, viz. the actual drinking of water for a period of hours before the experiment has, however, been prevented. In order to control this question of thirst in a satisfactory way, it is necessary to give a constant diet, limit the activities of the animal, and if possible keep it at a constant temperature. It was not possible to keep the animals at a constant temperature throughout the year, but this difficulty was overcome by the carrying out of numerous control experiments.

After the injection of the alcohol into the stomach, samples of blood of 5 to 7 c.c. were withdrawn at different intervals.[1] These intervals were short in the early stages, that is when the rate of absorption into the blood-

[1] Gréhant (*Compt. rend. Soc. de Biol.*, Par., 1899, **51**, 946, and 1900, **52**, 894) has used this method of making a series of analyses of alcohol in the blood at intervals.

stream was rapid, but were longer as the experiment proceeded. Samples were taken usually at half-hourly intervals during the first $1\frac{1}{2}$ hours, then at 1 hour, $1\frac{1}{2}$ hours, and 2 hours intervals.

The most satisfactory method of withdrawing blood is to make a small cut of about $\frac{1}{8}$ in. depth at the edge of the ear and allow the blood to drop into a weighing bottle. When the requisite quantity is obtained, the cut is held with cotton wool until coagulation is produced. Further samples can be easily obtained from the same cut after rubbing off the clot.

This method is easy and has many advantages over the withdrawal of blood by venepuncture in the case of dogs. The weighing bottles into which the blood was dropped each contained 1 c.c. of 7 per cent. sodium citrate solution. This effectively prevented blood coagulation. The estimation of the alcohol in the samples of blood was started as soon as possible after withdrawal. This usually took place on the day following the animal experiment. Overnight the blood was kept in a cold place. In hot weather it was necessary to keep the blood in an ice-chest until distilled.

Estimation of Alcohol in the Blood.

For the estimation of alcohol in the blood the method adopted by Pringsheim [1] was used. The blood was distilled under reduced pressure, the distillate was then heated up in a stoppered bottle with a standard solution of $K_2Cr_2O_7$ and, after cooling, the excess of potassium bichromate not reduced by the alcohol was estimated by titrating with an acid solution of ferrous ammonium sulphate.

This method has slowly evolved as the result of many researches on alcohol by different investigators. Bodländer [2] appears to have first used $K_2Cr_2O_7$ and H_2SO_4 for oxidizing the alcohol. Cotte [3] was the first to titrate with ferrous ammonium sulphate, using $K_3FeC_6N_6$ as an indicator. An historical account of the development of the method is given by Pringsheim.

Strengths of solutions and the general technique employed followed closely the recommendations of Pringsheim. The potassium bichromate solution contained 14·725 grammes in 2 litres. Pringsheim [1] states that 22·6 c.c. of this solution is reduced by 50 cm. of alcohol, and this figure has been used in the calculations.

The ferrous ammonium sulphate solution contained 39·24 grammes of this substance in 2 litres, and to this was then added 100 c.c. of concentrated sulphuric acid. Standarized against the $K_2Cr_2O_7$ solution it was found that 20 c.c. of the latter was equivalent to about 63 c.c. of the ferrous ammonium sulphate solution. Although the presence of the sulphuric acid conferred stability on the ferrous ammonium sulphate solution, the two solutions were compared in every experiment lest any alteration in strength had taken place.

The blood was washed from the weighing bottles into a litre flask which was connected up to a double surface condenser. The distillate was received into a large boiling-tube surrounded by an ice-salt mixture. Between this tube and the water-pump another tube was placed containing about 10 c.c. of water also surrounded by ice. Air was evacuated by the pump and the blood allowed to distil at a temperature of 50°–55° C. The greatest trouble met with in this work was the constant frothing up of the blood. The trouble was never overcome, and in every distillation the blood had to be carefully watched. A stream of air was allowed to play on the froth when it got too high in the flask. No trace of blood other than its volatile contents must be allowed to pass from the flask into the distillate. If some of the froth bubbles over, the whole lot must be re-distilled until a clear colourless distillate is obtained. The blood was distilled almost to dryness, and the condenser then well washed with distilled water and the washings added to the distillate. To this also was added the water from the second test-tube through which the air had been drawn. The washings and distillate were placed in

[1] Pringsheim, *Biochem. Ztschr.*, Berl., 1908, **12**, 141.
[2] Bodländer, *Arch. f. d. ges. Physiol.*, 1883, **32**.
[3] Cotte, Abstract in *Chem. Ztschr.*, **21**, 254, referred to by Pringsheim.

a reagent bottle, 20 c.c. of the standard $K_2Cr_2O_7$ was then added, together with 4 c.c. of concentrated sulphuric acid. After shaking, a cork was tied in the bottle, and this was then heated in a water bath at 100° C. for $1\frac{1}{4}$ hours. After cooling, the solution was titrated with ferrous ammonium sulphate. The end-point for this titration requires experience before absolutely reliable results are obtained. Ferrous ammonium sulphate is added to the bichromate mixture until the green colour just turns blue. The end-point is reached if a drop of freshly-prepared solution of potassium ferricyanide meeting a drop of the mixture being tested, on a filter paper, causes a faint prussian blue to develop. The ferrous ammonium sulphate solution is added drop by drop at this stage until the prussian blue reaction on the filter paper is obtained. It is difficult at first to appreciate the slight differences between the various shades intermediate between real green and undoubted blue, but experience overcomes this difficulty. Considering the small amounts of alcohol in the blood, the method gives fairly accurate results.

The researches of previous workers on this subject have made it clear that the blood always contains a small quantity of a volatile reducing substance which may be alcohol. For instance Schweisheimer[1] states that these reducing agents are equivalent to quantities of alcohol varying from 0·02955 per mille to 0·03686 per mille. Rosemann[2] suggests that, if alcohol, it is probably due to bacterial decomposition in the intestine. In any case the amount is too small to have any interfering action on the experimental results to be recorded.

III. Relation between Alcohol in Blood and the Amount drunk.

Fig. I illustrates the varying concentration to which alcohol in the blood attains according to the quantity taken. The following tables representing the results recorded in Fig. I, together with similar experiments on other dogs, will probably indicate more clearly the relation between the alcoholic concentration in the blood at its maximum and the amount drunk.

Amount of alcohol taken.	Maximum concentration in blood cm. per 100 grammes blood.	Time after taking alcohol.	Alcohol in blood at maximum point per 10 c.c. of alcohol drunk.
Large brown.	*Weight* 13 *kilograms.*		
55 c.c.	464 cm.	2 hours	84 cm.
50	445	1	89
30	265	$1\frac{1}{2}$	88
20	153	$1\frac{1}{4}$	77
Large black.	*Weight* 12 *kilograms.*		
50 c.c.	447 cm.	2 hours	89 cm.
30	277	$2\frac{1}{4}$	92
Small black.	*Weight* 10 *kilograms.*		
40 c.c.	530 cm.	$1\frac{1}{2}$ hours	132 cm.
30	398	$1\frac{3}{4}$	133
20	243	$1\frac{1}{2}$	121
Small white.	*Weight* $10\frac{1}{2}$ *kilograms.*		
40 c.c.	504 cm.	1 hour	126 cm.
30	387	1 hour	129

[1] Schweisheimer, *Deutsches Arch. f. klin. Med.*, Leipz., 1913, 109.
[2] Rosemann, *Oppenheimers Handbuch der Biochemie*, 1911, 4 (1), 422.

As regards the maximum concentration it will be seen:

(1) That when the alcohol taken varies between 55 c.c. and 30 c.c., the amount in the blood at its maximum is proportional to the amount taken.

(2) That when the alcohol is taken in smaller amounts, i.e. 20 c.c., then this relationship no longer holds, and there is less in the blood than would be expected. It appears as if some demand was first made on the small quantity of alcohol by some other tissues before the blood received its portion. Part of this difference can also be explained by the proportionate greater loss by oxidation during the period before the maximum is attained in those experiments when smaller quantities of alcohol were given.

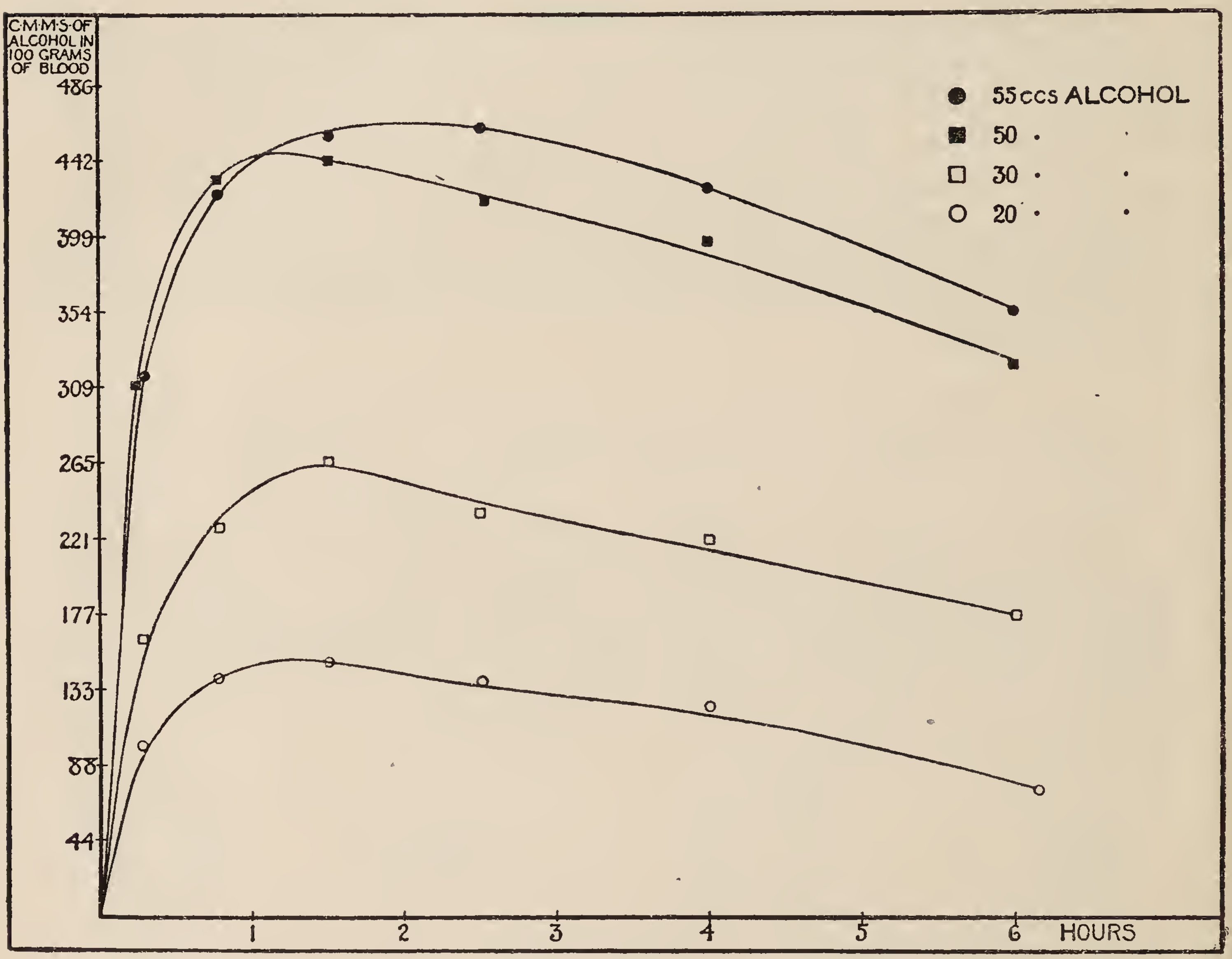

FIGURE I.

It will be further observed that the amount of alcohol in the blood of the different dogs after drinking equal quantities of alcohol is not proportional to their body weights. The smallest of these dogs received an average increased concentration of 128 cm. per 100 grammes of blood for each 10 c.c. of alcohol drunk, and the largest an increase of 84 cm. for the same amount. The weights of these dogs were respectively 10·5 kilograms and 13 kilograms, so that the amount of alcohol in the blood is not inversely proportional to the dogs' weight, but the amount in the blood of the smaller dog is relatively much higher than in the larger one. Assuming that the results obtained in these particular dogs are not a coincidence, and further, if the supposition is accepted that there is a relationship between alcohol in the blood and intoxication,

then the smaller animal would be expected to be more intoxicated with a less quantity of alcohol than its weight would demand. It was certainly the case with these dogs that the smaller animals became more intoxicated with proportionately less alcohol than the heavier dogs. Applying such results to men, other conditions such as tolerance, &c., being equal, it is probable that if a small and a big man drank quantities of alcohol proportional to their weights, the former would be intoxicated at a time when the latter would be sober.

It is interesting also to notice the alcoholic relationships in each particular dog when in a fat and a lean condition. At one period of the work the dogs lost weight and at a later period became much fatter. The following figures illustrate the alcohol distribution in the lean and fat conditions:

Small black.

May, 1918.	Weight 10 kilograms.	Increased amount of alcohol in blood at maximum per 10 c.c. taken	= 133 cm. per 100 grammes blood.
August, 1918.	Weight 11 kilograms.	,,	= 118 ,,

Ratio of body weights of dog $= \frac{10}{11} = 0{\cdot}91$

Inverse ratio of alcohol concentrations $= \frac{118}{133} = 0{\cdot}90$

Large brown.

May, 1918.	Weight 11·75 kilograms.	Increased amount of alcohol in blood at maximum per 10 c.c. taken	$= \frac{475}{5} = 92$ cm. per 100 grammes blood
August, 1918.	Weight 13·5 kilograms.	,,	$= \frac{420}{5} = 84$,,

Ratio of body weights of dog $= \frac{11{\cdot}75}{13{\cdot}5} = 0{\cdot}87$

Inverse ratio of alcohol concentrations $= \frac{84}{92} = 0{\cdot}91$

In the case of each dog the ratio of the alcohol concentration in the blood to the body weight is practically constant, whether it be in a fat or a lean condition, or, in other words, the amount of alcohol in the blood per unit of alcohol drunk in any single dog when its weight alters is inversely proportional to its weight.

The reaction to alcohol, therefore, in the case of an animal whose weight varies is not the same as when a comparison is made between a small or a larger animal. In the individual animal, the amount of alcohol in the blood varies inversely as its weight alters, whereas in comparing different animals, the smaller one accumulates a greater concentration of alcohol in its blood than its weight would warrant when quantities of alcohol proportional to body weight are taken by mouth.

It has been pointed out by Gréhant[1] that the amount of alcohol in the blood of an animal after a definite quantity has been drunk

[1] Grehant, *Compt. rend. Soc. de Biol.*, Par., 1881, 1896, 1899.

is the amount that would be expected assuming that the alcohol is evenly distributed throughout the body. For instance when his dogs received 5 c.c. and 4 c.c. of alcohol per kilo body weight, the alcohol content of the blood was respectively 0·5 per cent. and 0·4 per cent. In my experiments the weight of the brown dog was 13·5 kilograms, and the amount of alcohol in 100 grammes of blood for each 50 c.c. of alcohol drunk was 420 cm. On the above assumption the blood ought to have contained 370 cm. With a smaller dog, viz. small black, the discrepancy is rather greater, the actual amount of alcohol in the blood at its maximum being 354 cm. per 100 grammes of blood and the theoretical quantity being 273 cm. It would appear, therefore, that Gréhant's results are of the nature of a coincidence, and that there is not a sufficient basis to warrant the general assumption as above expressed being applied to all dogs.

Summary.

(1) In any individual dog, the amount of alcohol in unit volume of blood at its maximum is proportional to the amount drunk if taken with stomach and small intestine empty. This only holds if the alcohol drunk is greater than 2 c.c. per kilogram weight. Below this there is less alcohol in the blood.

(2) Comparing a large and a small dog, if both receive an amount of alcohol proportional to their body weight, the blood of the smaller dog contains at its maximum a relatively larger amount of alcohol in unit volume.

(3) If a dog varies in weight, then, after receiving the same amount of alcohol on different occasions, the amount in unit volume of blood is inversely proportional to its body weight.

IV. The Rate of Disappearance of Alcohol from the Blood.

Fig. I shows, as in fact do all the curves, how slow is the rate of disappearance of alcohol from the blood compared to its rate of accumulation. This point is, however, most evident in Fig II, where the experiment was continued for about 20 hours It will be seen in Curve A that, after taking 50 c.c. of alcohol, this substance reaches a maximum in an hour, but that, even at the end of 19 hours, some remains in the blood, i. e about 33 cm. per 100 grammes of blood. It might be thought that this small amount represented an error in estimation, and in order to determine this point a further injection of 50 c.c. of alcohol was again given 18½ hours after the first injection. Curve B is the result obtained after this second injection of alcohol. It will be seen that a higher concentration of alcohol in the blood is produced than on the previous day, the difference being no doubt due to the small amount remaining from the first injection. Here, then, we have an accumulative effect produced by a second alcoholic injection in consequence of the fact that the first 50 c.c. had not been fully oxidized by the animal in 18½ hours. It may be further mentioned that evidence of an accumulative effect was also

obtained in the more marked intoxication of the dog following the second day's injection. In the case of this dog, we have an animal, whose weight is 13·5 kilograms, taking 20 hours to get rid of 50 c.c. of alcohol from its blood, and presumably therefore from its body, that is, at the rate of $2\frac{1}{2}$ c.c. per hour or 0·185 c.c. per kilogram weight per hour. This slow rate of disappearance of alcohol from the blood has been observed by Gréhant and other workers on the subject. It is a point of some importance, for it can readily be understood how easy it must be to produce intense intoxication by a second drink of an alcoholic beverage which, had it been the first drink, would have had no such result, although

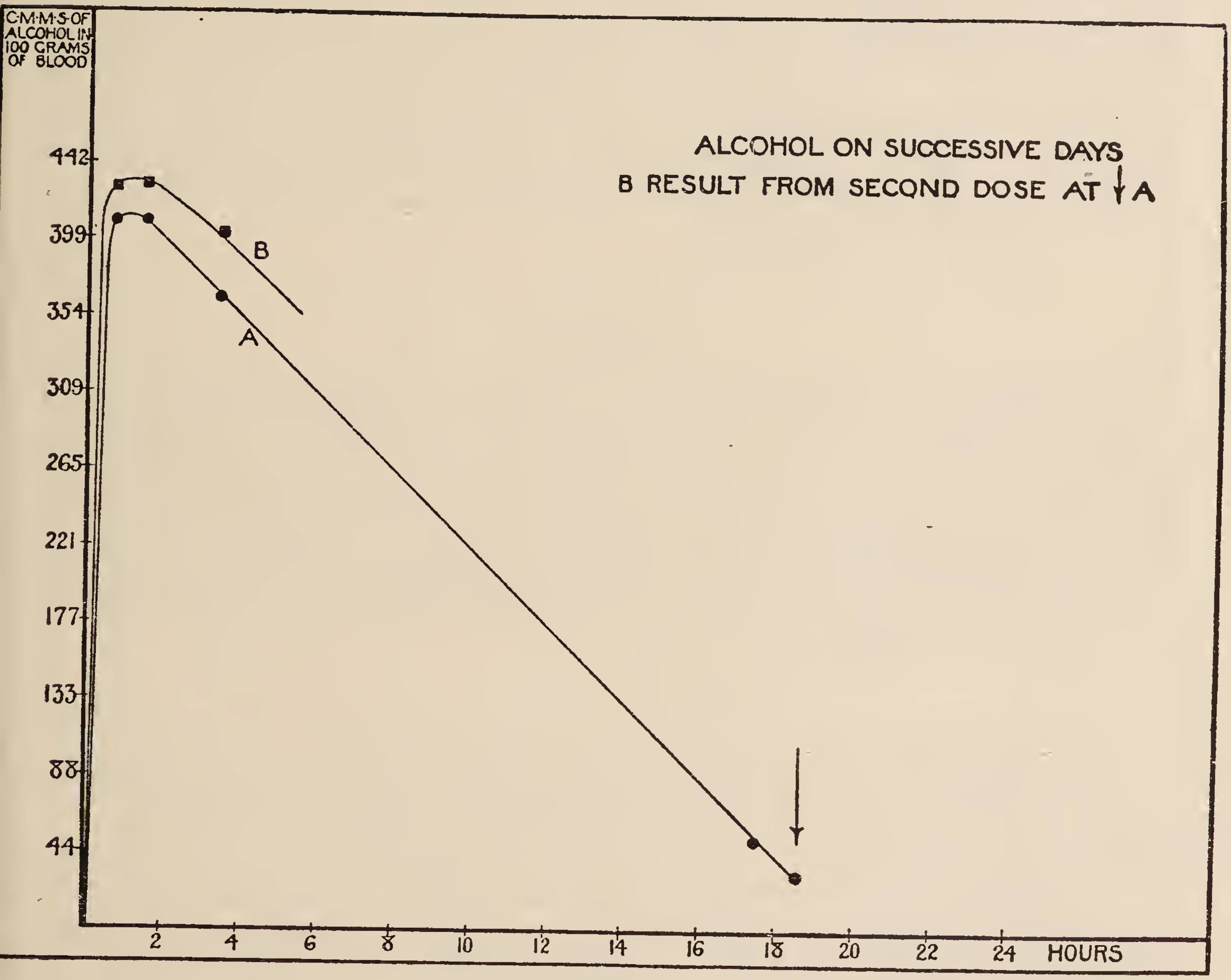

FIGURE II.

the interval between the drinks may have been many hours. This fact also forms, no doubt, part of the physiological basis of the feeling of ill-health on the morning following a carouse, and the gradual development of a feeling of well-being as the day progresses and the alcohol is cleared out of the body.

Calorimetric experiments, and more particularly those of Atwater and Benedict,[1] demonstrate that this disappearance of alcohol from the body involves its almost complete oxidation, so that we can speak of the oxidation of alcohol as being a slow process and going on at the rate of 0·185 c.c. per kilogram weight per hour in this particular dog's body.

Fig. II shows another point worthy of comment. After reaching a maximum the Curve A descends in a straight line to the abscissa.

[1] Atwater and Benedict, *Mem. Nat. Acad. Sc.*, Wash., 1902, **8**, 231.

This means that the rate of oxidation is constant throughout the whole period, and this is the case in spite of the fact that the amount of alcohol in the body is getting progressively less. The interpretation of this fact is therefore that, whatever the amount of alcohol in the body, the rate of oxidation is constant, or, in other words, the rate of oxidation of alcohol is independent of the amount drunk. Lest Curve A of Fig. II be regarded as a coincidence, reference to Fig. I will clearly corroborate this fact. In Fig. I we see curves representing the rates of oxidation of alcohol after 55, 50, 30, and 20 c.c. of alcohol respectively have been drunk by the same dog. There is a striking parallelism between the descent of the different curves which means that, in unit time, practically the same amount of alcohol is being oxidized in each case. Other evidence of the constancy of the alcohol oxidation and its independence of the amount in the body will be forthcoming in the course of this paper, and its further significance more fully discussed when alcohol is considered from the point of view of a food-stuff.

Summary.

The rate of accumulation of alcohol in the blood after entrance to the stomach is rapid, and reaches its maximum in ½ hour to 2 hours. The rate at which it leaves the body is slow, and is at the approximate rate of 0·185 c.c. per kilogram weight per hour. Thus a dog of 13·5 kilograms takes 20 hours to get rid of 50 c.c. of alcohol. This dog was not at rest throughout, but could move about a room at will.

V. The Effects of drinking a given Amount of Alcohol at once and in Portions taken at Different Times.

A common belief among those interested in alcoholic intoxication is that symptoms produced by a definite quantity of alcohol may be avoided to some extent if it is gulped, but that, if the same amount is drunk slowly or sipped, then the worst may happen. It is impossible to reproduce exactly and test by experiment this condition in an animal, but several attempts were made to simulate the condition by comparing the results following the giving to an animal all the alcohol at once, and in four portions at intervals of about 10 minutes. In no case was any evidence obtained that taking the alcohol in portions at short intervals increased the amount and rate of accumulation of alcohol in the blood. Nor did the symptoms of intoxication appear to be increased. It is difficult, therefore, to believe that taking alcohol at one gulp can have an effect very different from that which results when it is sipped over a period of 40 minutes.

Further experiments were made in which the intervals between the drinks were gradually lengthened, and the results are given in Fig. III. Here the same total quantity of alcohol was given under the following conditions:

A. 250 c.c. of a 20 per cent. solution of alcohol (i.e. 50 c.c. absolute alcohol) at once.
B. The same quantity in two equal portions at an interval of 3 hours.
C. The same quantity in three equal portions at intervals of 1 hour.
D. The same quantity in three equal portions at intervals of 2 hours.

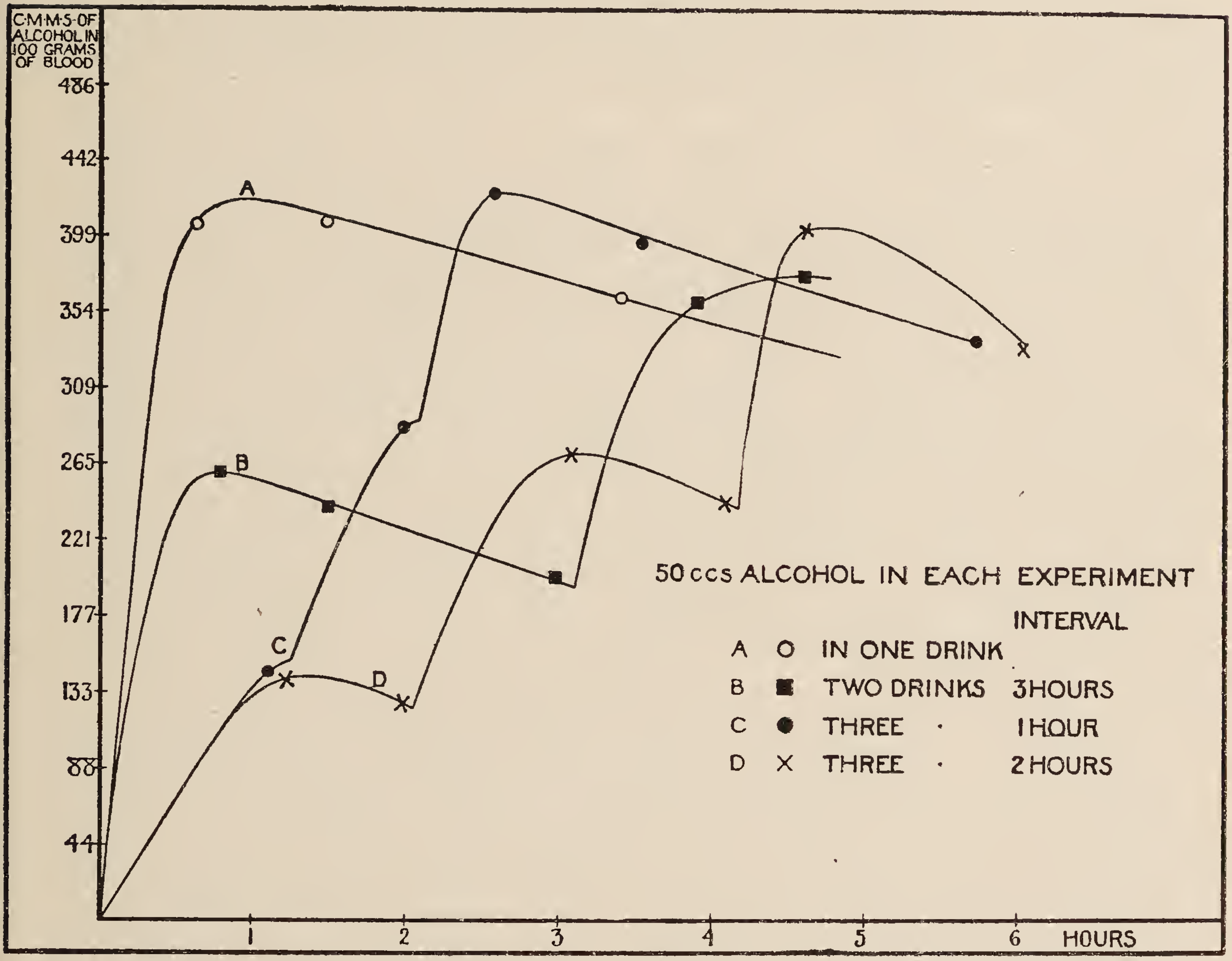

Figure III.

If we look at Curves A, C, and D we see the salient points to be:

(1) The same maximum concentration of alcohol is reached. Of course in each experiment the time of maximum concentration varies.
(2) The rate of accumulation of alcohol in the blood increases as the amount increases.
(3) The rate of accumulation when the alcohol in the blood approaches its maximum is approximately the same.
(4) At the end of each experiment, i.e. about 6 hours after the alcohol was first given, the amount remaining in the blood is practically the same.

If we now look at Curve B we see that these facts no longer hold, for (1) the maximum concentration in B is slightly lower than in A, C, D; (2) the rate of accumulation of alcohol in the

blood after the second drink (3 hours after the first) is much slower than after the second and third drinks of C and D.

These facts, which seem unexpected at first sight, involve several points of interest, and can only be understood when the effect of water on alimentary absorption is appreciated. This latter condition will be discussed later in the paper, but it may be well to consider the facts as expressed in Fig. III without offering any detailed explanation.

Alcohol, then, accumulates more rapidly as the amount in the blood increases when the interval between the drinks is not more than 3 hours. In Curve D (interval between drinks 2 hours), during the first 75 minutes of the experiment, 140 cm. of alcohol were added to 100 grm. blood, or $\frac{140}{75} = 1{\cdot}9$ cm. per minute. After the third injection of the same quantity of alcohol, 158 cm. were added to 100 grm. blood in 30 minutes, or 5·3 cm. per minute. It is clear also that this difference cannot be explained by assuming that, in the latter case, there was unabsorbed alcohol remaining over from the previous injections, for the shape of the earlier portions of the curve indicates that the first injection was completely or almost completely absorbed from the alimentary canal before the second injection was given, and the second injection before the third was given. It appears therefore that, under the conditions of the experiments C and D, the more alcohol there is in the blood the more easily is further alcohol absorbed into it from the alimentary canal. When, however, the interval between the drinks is 3 hours or longer, then there is no acceleration of absorption of the second drink, and in fact the rate is slowed.

The two results, (1) that the same maximum concentration of alcohol in the blood was reached, and (2) that at the end of each experiment there remained practically the same amount of alcohol in the dog's body, point to another fact, viz. that the rate at which alcohol disappears from the body is constant, and is independent of the amount of concentration. For instance, comparing Curves A and D, it is evident that for the first 2 hours in Curve A there is three times as much alcohol in the dog's body as in D, and in the next 2 hours one-third more, yet at the end of 6 hours the alcohol remaining is the same. If the tissues burned up the alcohol at a greater rate when more was present, then less alcohol would have been found in the blood at the end of A than C. This is not the case, and therefore the rate of combustion must be independent of the amount drunk.

The facts that, when the interval between the drinks is not longer than 3 hours the maximum concentration of the alcohol in the blood is ultimately the same, and that the rate of accumulation at and before the maximum point in each case is the same, are evidence that the intoxicating symptoms at their maximum will be similar. In other words, the symptoms of intoxication produced are no less when an intoxicating quantity of alcohol is taken in portions at intervals of 2 hours than when the same alcohol is drunk in one gulp. There is of course a postponement of the worst effect. At the beginning of these experiments it was

expected that, by giving the alcohol in portions, the rate of maximum accumulation after the third portion would be similar to the rate of absorption of the first portion, and therefore less intoxication might result. This has not proved to be the case except when the interval between the drinks is 3 hours or longer. With intervals of 2 hours or less the absorption of alcohol in one drink is stimulated by the absorption of the fluid of the previous drink. The increasing amount of alcohol in the blood accumulating at an increased rate brings about maximum intoxicating symptoms. When the interval is 3 hours or longer the absorption of the fluid of the first drink no longer stimulates the absorption of alcohol in the second drink, and a slower accumulation of alcohol in the blood takes place.

These results may at least be partially explained by later experiments in which the effect of drinking water on the subsequent absorption of alcohol was determined. It will be seen that, after water has been absorbed from an empty alimentary canal, it brings about such a state of affairs that alcohol is more rapidly absorbed than normally, and that this influence persists for 4 hours after the water has been drunk and possibly longer. In these experiments, however, the stimulation to absorption by the alcoholic solution was only obvious for 2 hours, and when the interval was 3 hours the second lot of alcohol was more slowly absorbed. Probably the difference between these results and those of the experiments with water depends on the different amount of fluid consumed in the different series. In the water experiments 500 c.c. were drunk, whereas in these experiments the greatest quantity of fluid taken at any period was never more than 125 c.c. The effect of the smaller quantity of fluid would probably disappear more rapidly than that produced by a larger quantity. It would appear probable that, if the experiments were repeated with more dilute fluids, e.g. beer, the intervals would have to be considerably longer than 3 hours if it were desired to do away with the stimulating factor of previous drinks and, by altering the rate of absorption of alcohol into the blood-stream, to lessen the symptoms of intoxication.

Summary.

These results show that the amount of alcohol in the blood at its maximum and the rate of accumulation immediately before this point is practically the same, whether an intoxicating dose of alcohol is drunk in one portion or in three portions at 1 or 2 hours intervals. When the interval was 3 hours, then, in this particular group of experiments, both the maximum point and the rate of accumulation were depressed.

VI. The Effect of Dilution.

The relative intoxicating values of strong and weak alcoholic solutions demanded investigation, and some of the results obtained in respect of the entry of alcohol into the blood when solutions of different strengths were taken will now be described. Fig. IV is a representative result of experiments on one dog.

In Curve A 40 c.c. of alcohol were given in a 20 per cent. strength.
,, B 40 ,, ,, ,, ,, 5 ,, ,,
,, C 30 ,, ,, ,, ,, 20 ,, ,,
,, D 30 ,, ,, ,, ,, 5 ,, ,,

From the point of view of dilution, therefore, A and B are comparable, similarly C and D. It is evident that, whereas there is a distinct difference between A and B, there is but little between C and D. The maximum concentration in the blood in B does not approach the maximum concentration of A, and altogether there is throughout the period of the experiment, less alcoholic concentration in the blood when the alcohol was taken in the dilute form.

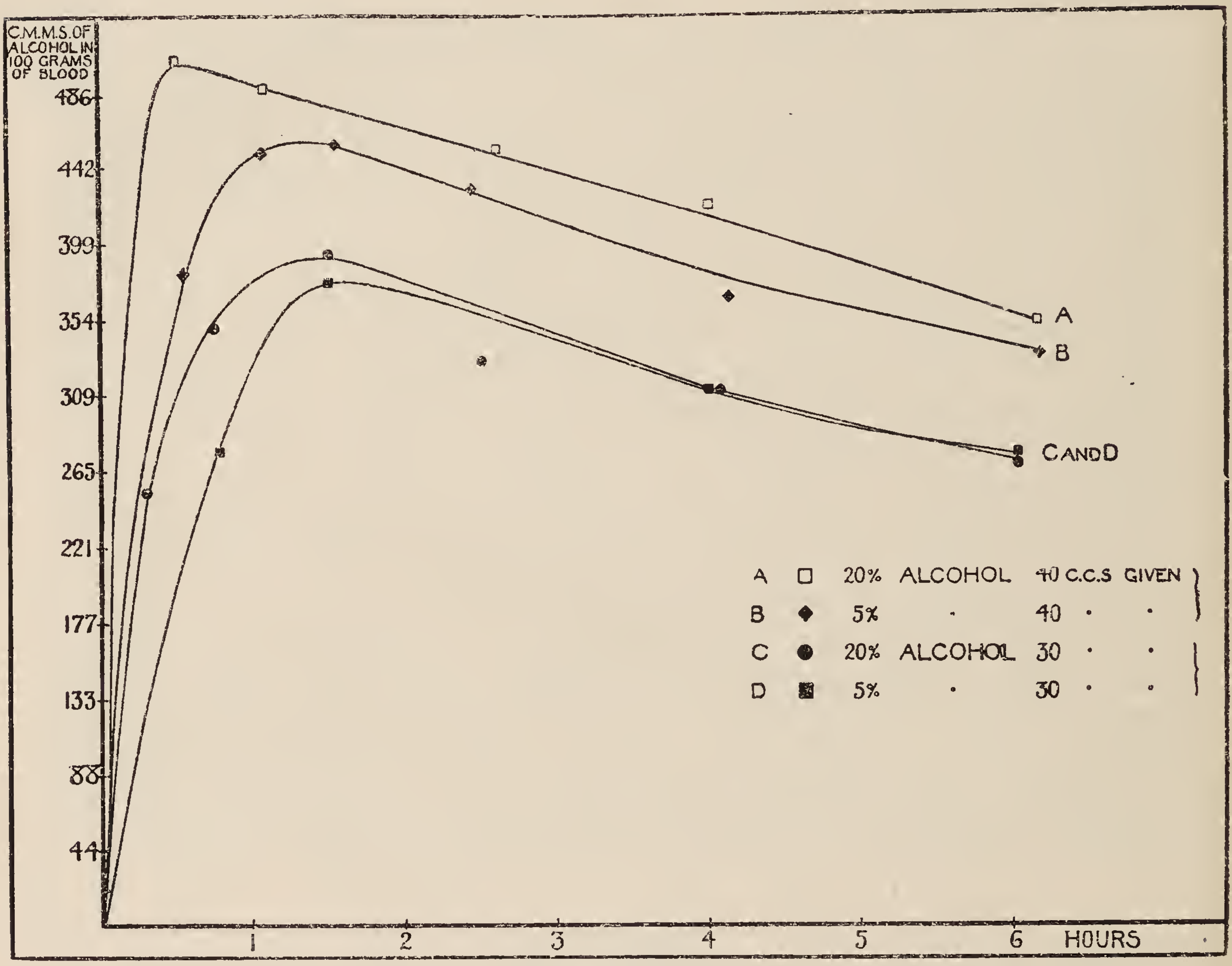

FIGURE IV.

It may be well to point out that the time element so far as drinking was concerned plays practically no part in the experiments. That is to say, even in experiment B, where it was necessary to give 800 c.c. of fluid, this was all placed in the stomach in the course of 3 or 4 minutes. The differences therefore in Curves A and B are entirely due to the different rates of absorption of strong and weak alcohol solutions when all the alcohol was present in the alimentary canal in each case. Stronger solutions of alcohol were also tried, but were not continued because they tended to irritate the stomach and cause vomiting, whereas weaker solutions than 5 per cent. were not practicable because of the difficulty of getting a larger bulk of fluid into the stomach within a few minutes.

The intoxicating symptoms produced by the weak and strong solutions were as might be expected from the curves. That is to say, in each case the dilute fluids produced less intoxication than the strong fluids containing corresponding amounts of alcohol. Whereas, however, there was a pronounced difference in the dog's condition in Curves A and B respectively, the difference was slight between C and D. This fact is the general rule, viz. that the greater the amount of alcohol taken, the greater is the difference between the intoxication symptoms and the blood alcohol when strong and dilute solutions are drunk. It is difficult to suggest a satisfactory explanation of this fact, but, speaking in general terms, it is probable that drinking a large bulk of fluid containing much diluted alcohol causes an increase in the general body fluids and a corresponding diminution in concentration of the alcohol present in the tissues and tissue fluids. With the elimination of this fluid through the kidneys and a restoration of the previous balance, it would be expected, unless, indeed, there is also an increased excretion of alcohol through the kidneys at the same time, that the alcohol present in the blood would ultimately be the same in whatever form of dilution strong and dilute solutions of alcohol were drunk. These experiments further show that this period of equality would only occur after the alcohol in the blood had passed its maximum and the worst symptoms of intoxication had passed off.

As for the slower rate of absorption of alcohol from the more dilute solutions, this can be easily understood. To get a concentration of x alcohol in the blood it would be necessary to absorb y c.c. of a 20 per cent. solution from the alimentary canal. To get the same concentration x after drinking a 5 per cent. alcohol solution, the alimentary canal would have to absorb $4y$ c.c. of solution. The difficulty of doing this in the short time that it takes to reach a maximum when a 20 per cent. alcohol solution is drunk, i.e. about 45 minutes, is obvious. This difficulty of arriving at the necessary maximum would be progressively greater with more dilute solutions than 5 per cent.

It is true of course that, in comparing 20 per cent. and 5 per cent. solutions of alcohol, the alcohol in the former might well have an inhibitory effect on absorption, so that the difference in time between the absorption of 1 vol. of 20 per cent. and 4 vols. of 5 per cent. might not be so great as 4 to 1. If, however, a comparison were made between a 5 per cent. and a 3 per cent. solution of alcohol, it is probable that a greater difference in the relative rates of alcohol absorption would be found, as the inhibitory effect of the alcohol would be small in both cases, and this difference would depend only on the relative power of absorbing proportions of water in the ratio 3 : 5.

Summary.

Comparing a 20 per cent. with a 5 per cent. solution of alcohol, when the same amounts of alcohol are drunk, the alcohol of the dilute solution is absorbed more slowly and attains a lower maximum in the blood than that of the strong solution. The difference is small when small quantities of alcohol are consumed, but becomes greater as the amount of alcohol increases.

VII. The Absorption of Alcohol in Different Beverages.

From the results obtained with dilute and strong solutions of alcohol, it might be expected that there would be some difference between the effect of spirits and beer. This is the case as can be seen in Fig. V.

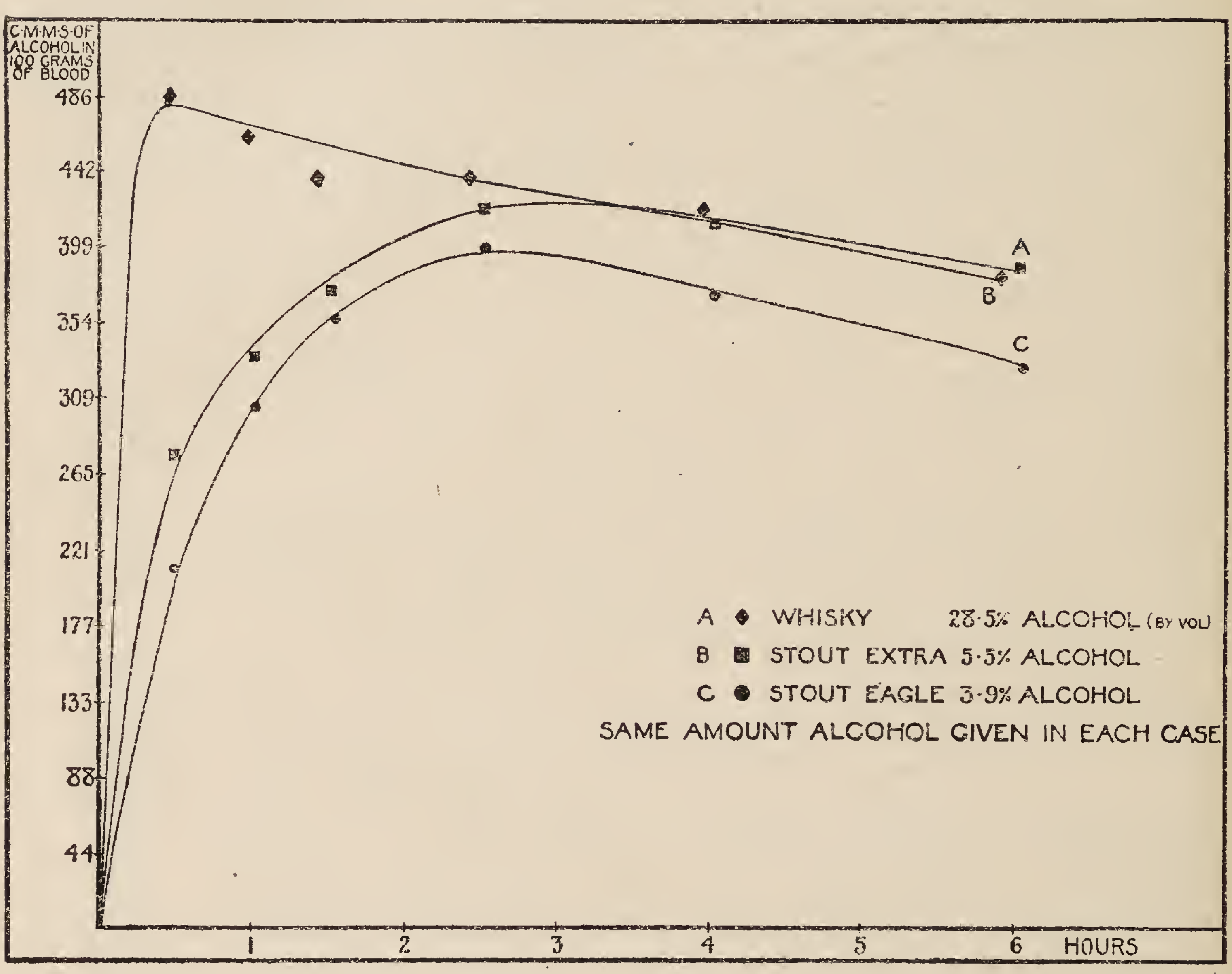

Figure V.

In Curve A 174 c.c. of whisky (28·5 per cent. alcohol by volume) were given.

In Curve B 910 c.c. of stout I (5·5 per cent. alcohol by volume) were given.

In Curve C 1,282 c.c. of stout II (3·9 per cent. alcohol by volume) were given.

In each experiment 50 c.c. of alcohol were given. The results obtained were strikingly different, the rate of absorption of the alcohol of the whisky being much greater and the maximum concentration in the blood being higher than in the stout experiments. Similarly, the weaker stout C (3·9 per cent.) produced lower alcohol in the blood throughout than stout B (5·5 per cent.). So marked was the difference in the intoxicating symptoms and the alcohol of the blood in the whisky and stout experiments respectively, that it appeared probable that some factor other than that of dilution was playing a part. In order to determine whether this was the case, the experiments detailed in Fig. VI were made. In these experiments, the whisky was diluted down to the strength

of the stout so that each contained 5·5 per cent. alcohol by volume. There is but little difference in the points of maximum concentration of alcohol in the blood in Curves A and B (Fig. VI), but there is a considerable difference between the rates of absorption of alcohol into the blood-stream in the two cases. In the case of the

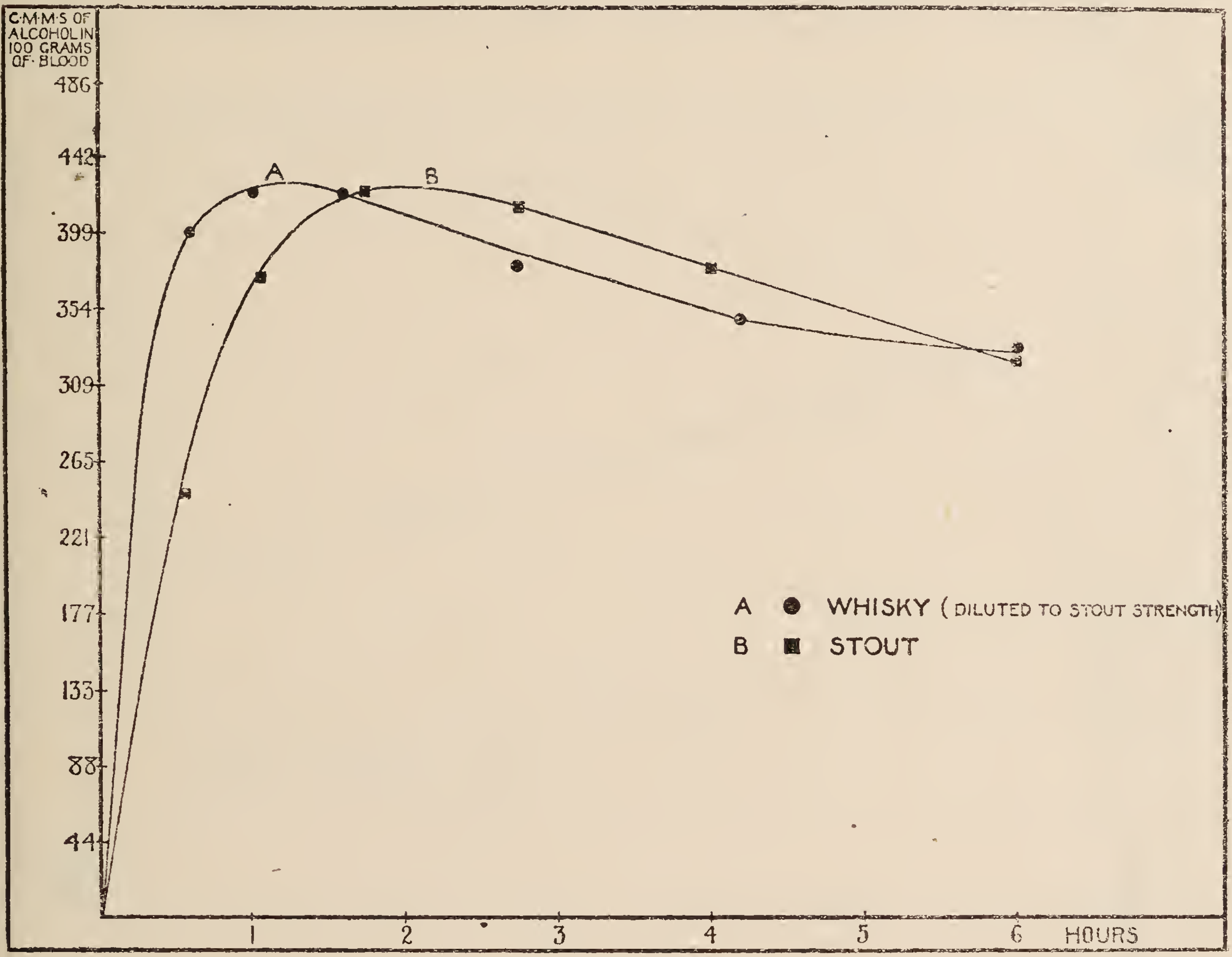

FIGURE VI.

diluted whisky the maximum concentration was reached $1\frac{1}{4}$ hours after the experiment started, in the case of the stout the maximum was only reached after 2 hours. It appears, therefore, that either whisky contains something which hastens alcoholic absorption or, what is more probable, that stout contains something which tends to delay absorption. It may be further remarked that, although the maximum amount of alcohol attained in each experiment was almost the same after the diluted whisky and the stout, it is undoubted that the symptoms of intoxication were more marked when the alcohol was more rapidly absorbed, i. e. in the case of the diluted whisky. What the component of the stout is which is capable of inhibiting the absorption of alcohol cannot be stated. It seemed possible that the substance conferring upon stout its colloidal nature was responsible, and, in order to determine this, 3 per cent. gum arabic was added to a solution of alcohol and the rate of absorption was compared to a solution of alcohol of similar strength without gum. Fig. VII shows that the gum in this experiment had no effect on the rate of absorption of alcohol. Similar experiments were made with starch as the colloid, but the results again were negative.

Summary.

The alcohol in stout is absorbed more slowly, and reaches a lower maximum in the blood than that of whisky. This is due to two conditions:

(1) The dilution of the alcohol in stout as compared with whisky.

(2) Stout contains something which inhibits absorption of its alcohol.

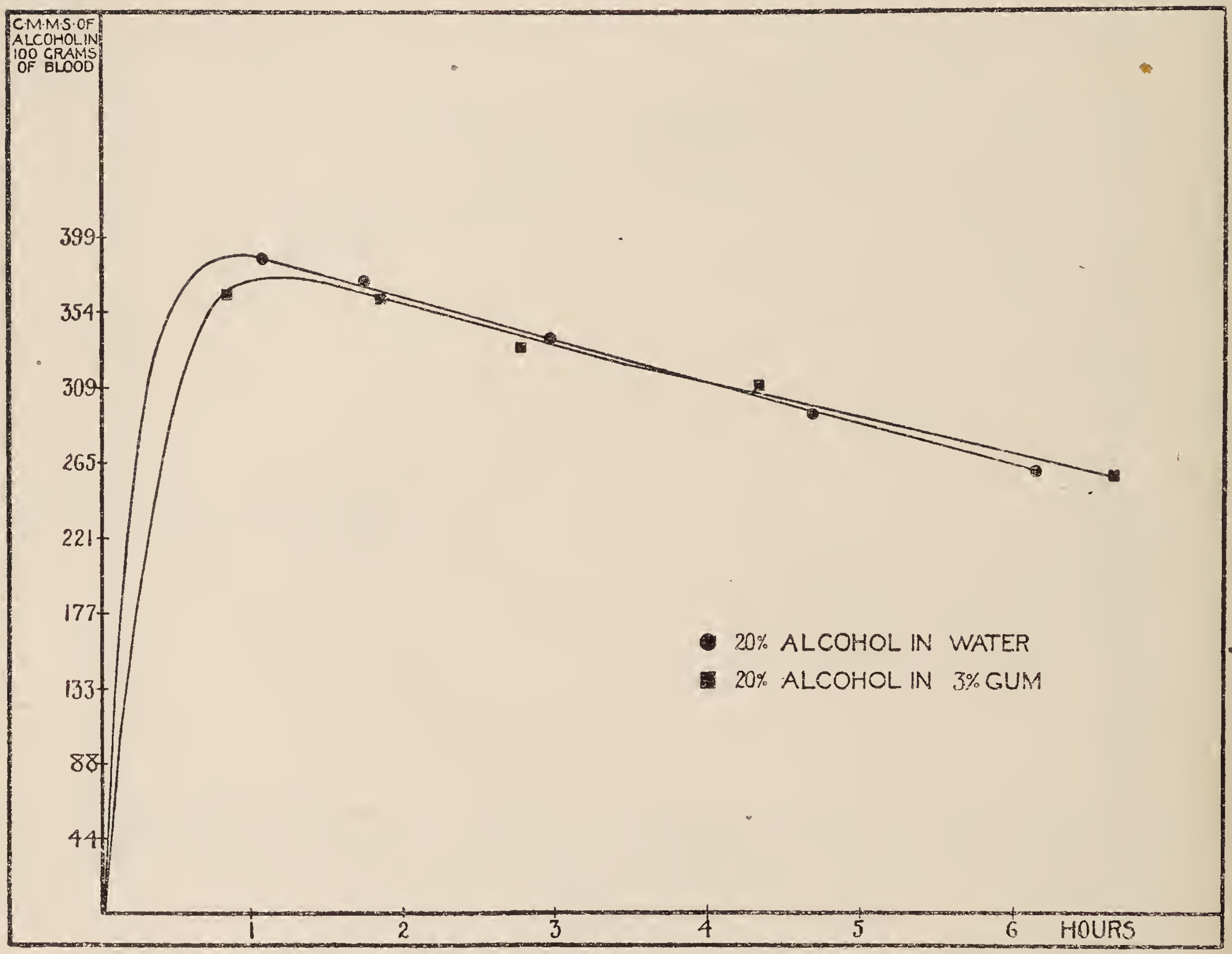

FIGURE VII.

VIII. THE EFFECT OF FOOD IN THE ALIMENTARY CANAL ON THE ABSORPTION OF ALCOHOL.

(a) *Bread and Milk.*

The effect of a meal of bread and milk on the absorption of alcohol is seen in Fig. VIII, which is typical of similar experiments made on the different dogs. The effect of eating such a meal is most marked when it is eaten less than 2 or 3 hours before the alcohol. With the lengthening of this period the curves more closely approximate to that of the control condition where no food has been taken for 20 hours. It will be noted that the portion of the curve most affected is that recording the first 3 hours of the experiment. During this period the curve is more flattened, so that not only is the maximum concentration of alcohol in the blood much lower than in the control curve, but also the rate of absorption is slower. As would be expected, therefore, the

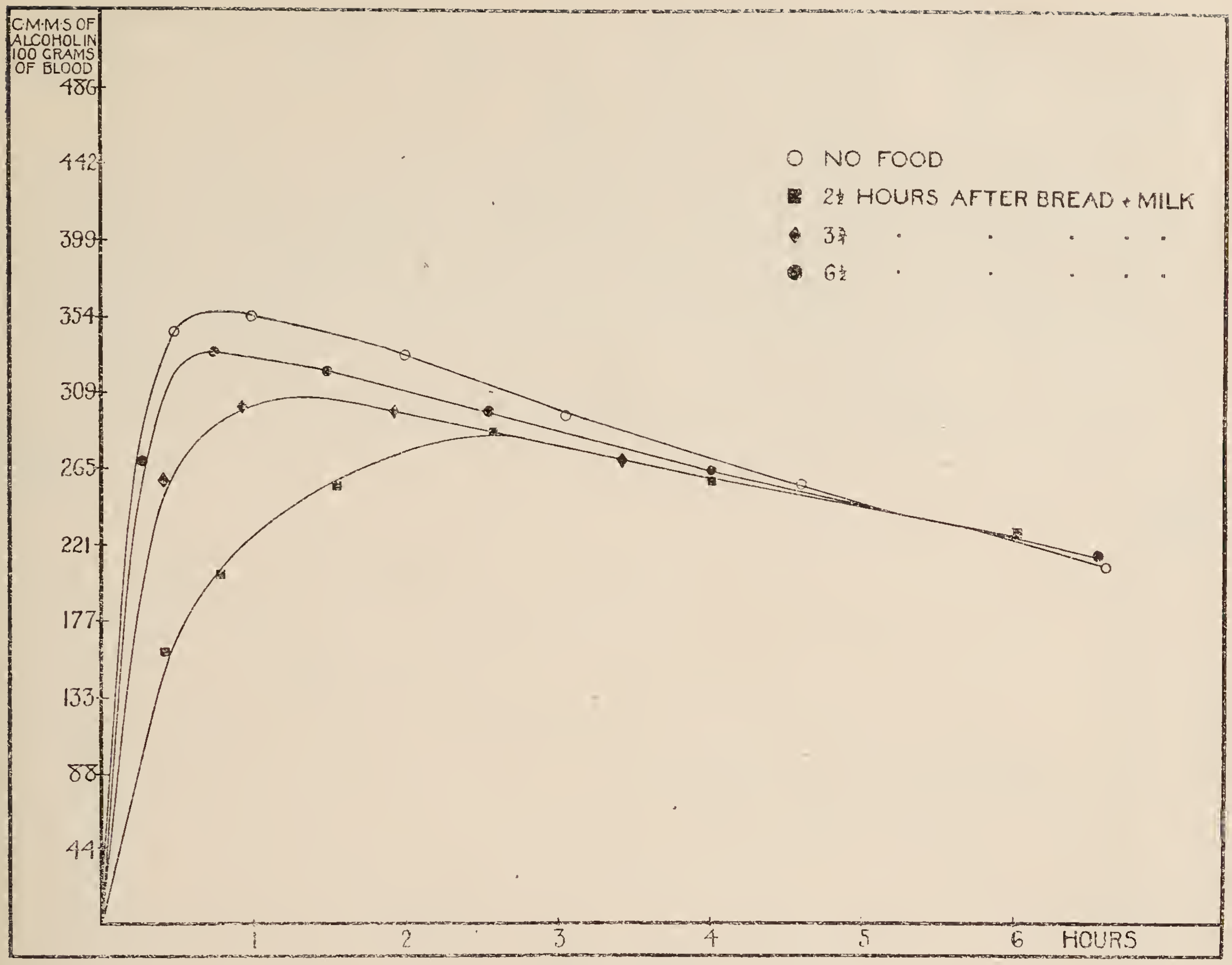

FIGURE VIII.

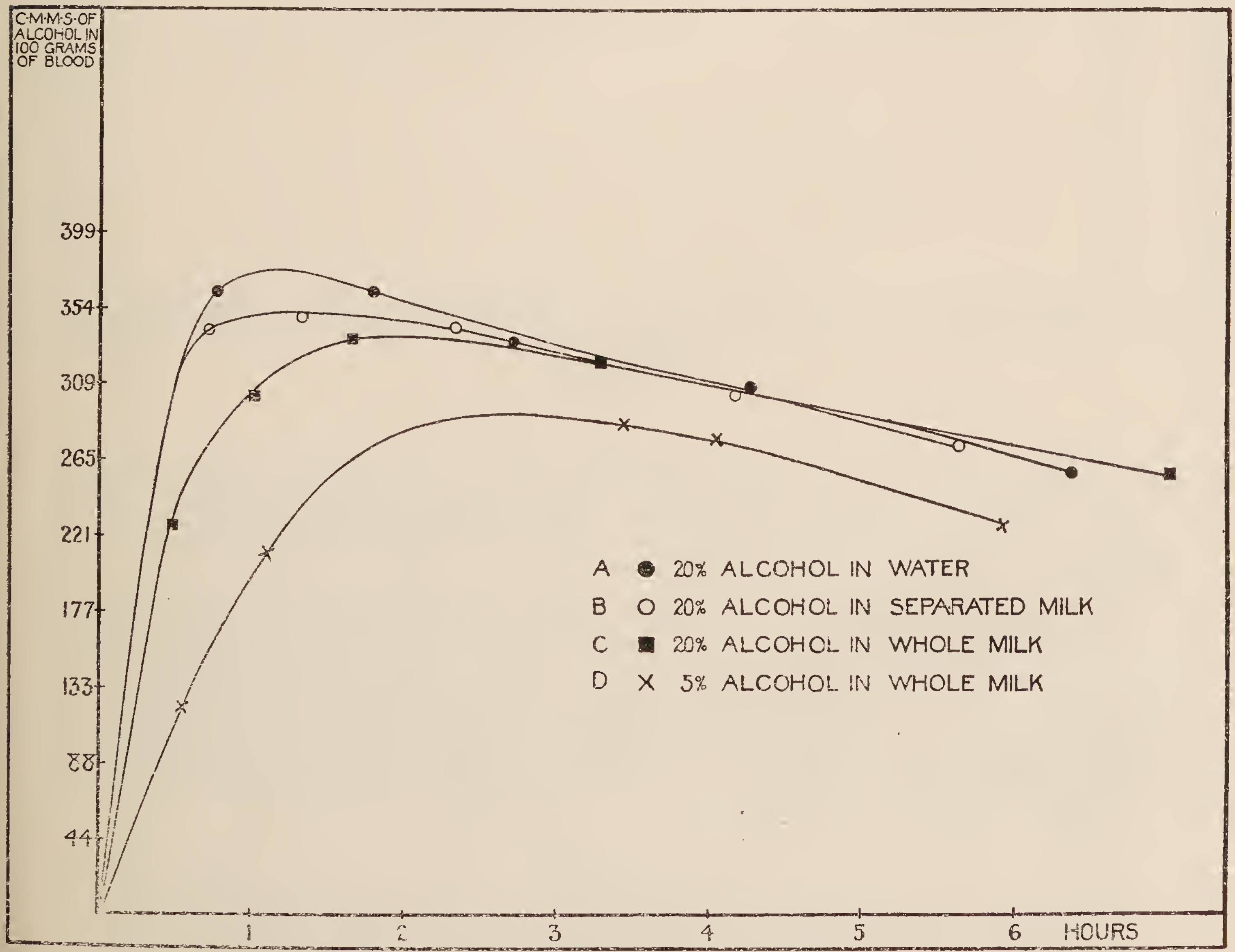

FIGURE IX.

period of maximum intoxication is very greatly reduced by a meal of bread and milk taken before the alcohol. It seemed likely that the effective part of the substances eaten was the milk, and this proved to be the case.

The inhibitory action of milk on the absorption of alcohol from the alimentary canal can also be obtained when the milk is added to the alcohol, and even when only small quantities of milk are used. Fig. IX shows this point. In Curve C 120 c.c. of milk were added to the alcohol, so that the total volume of fluid imbibed was 150 c.c.; in Curve B the same amount of milk was deprived of fat by a separating process before being added to the alcohol.

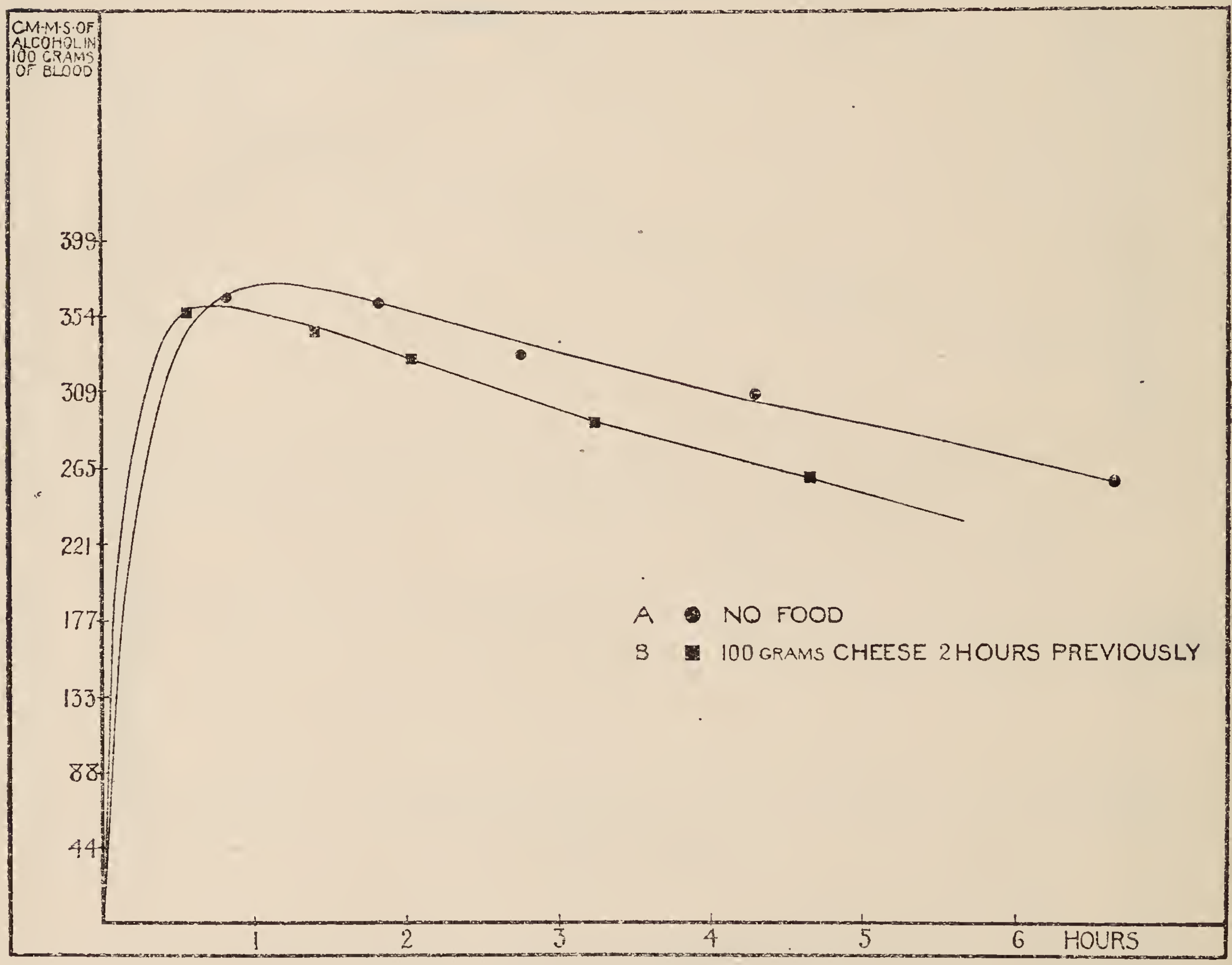

FIGURE X.

In each case there is a depressant effect produced by the milk. The whole milk was more effective than the separated milk. This point indicates that the milk fat plays an important part in this action.

In Curve D 560 c.c. of whole milk were added to the alcohol, so that in addition to its own action the element of dilution was also introduced into the experiment. It is therefore not surprising that this curve should be so relatively flattened. The reduction in the intoxication caused by adding a large quantity of milk to the alcohol is very striking.

(*b*) *Cheese.*

In view of the effect of milk it was thought desirable to see if cheese had a similar action in altering the curve of absorption

and lowering intoxication. The type of cheese used cannot be stated, but it was an ordinary brand procurable in these times. It may therefore have contained little or no fat. The result of eating 100 grammes of this cheese 2 hours before the alcohol was taken is seen in Fig. X. The cheese had little or no influence on the rate of absorption, but brought about a slight lowering in the maximum concentration. It may be, therefore, that a small part of the milk effect may be obtained with cheese, but by no means the whole effect.

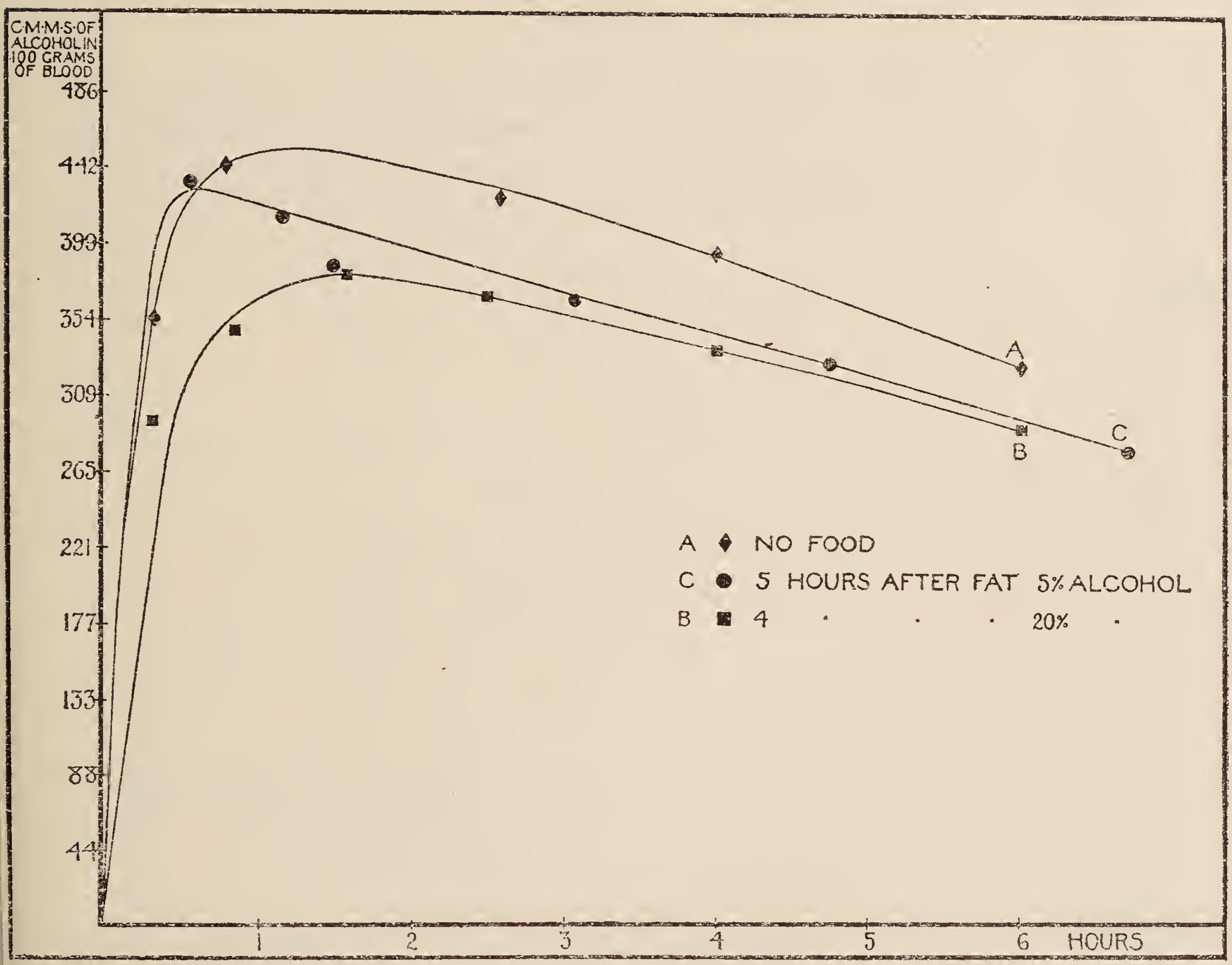

FIGURE XI.

(c) *Fat.*

The effect of eating fat before alcohol is shown in Fig. XI. Curve A is the control (no food) curve obtained after giving 50 c.c. in a 20 per cent. solution. Curve B was obtained after giving 50 c.c. of alcohol in a 20 per cent. solution following 100 grammes of suet eaten 4 hours previously. In Curve C the same amount of alcohol was given in a more dilute (5 per cent.) form also following a meal of fat. It will be observed that in the case of the 20 per cent. solution of alcohol, the rate of absorption is less and the maximum point of alcohol concentration in the blood depressed by the fat. When the dilute solution of alcohol was given, no depression of the rate of absorption was apparent, and, in fact, the absorption was rather more rapid than in the experiment without food. In view of the action of milk fat seen above it is probable that lower melting-

point fats, such as linseed or olive oils, would have produced more emphatic results.

It appears, then, that whereas fat has a depressing effect on the absorption of a 20 per cent. solution of alcohol, it has no such effect on a 5 per cent. solution. The explanation of this may be that the fat enters into a physical relation with the stronger solution, and so inhibits the absorption. With a 5 per cent. solution probably no such physical combination is possible, and the rate of absorption is unaffected.

(*d*) *Meat.*

The effect of eating meat prior to the taking of alcohol can be seen in Fig. XII. A half-pound of minced, lean beef was eaten by the dog 2 hours before receiving 250 c.c. of 20 per cent. alcohol. In the control experiment the same amount of alcohol was taken

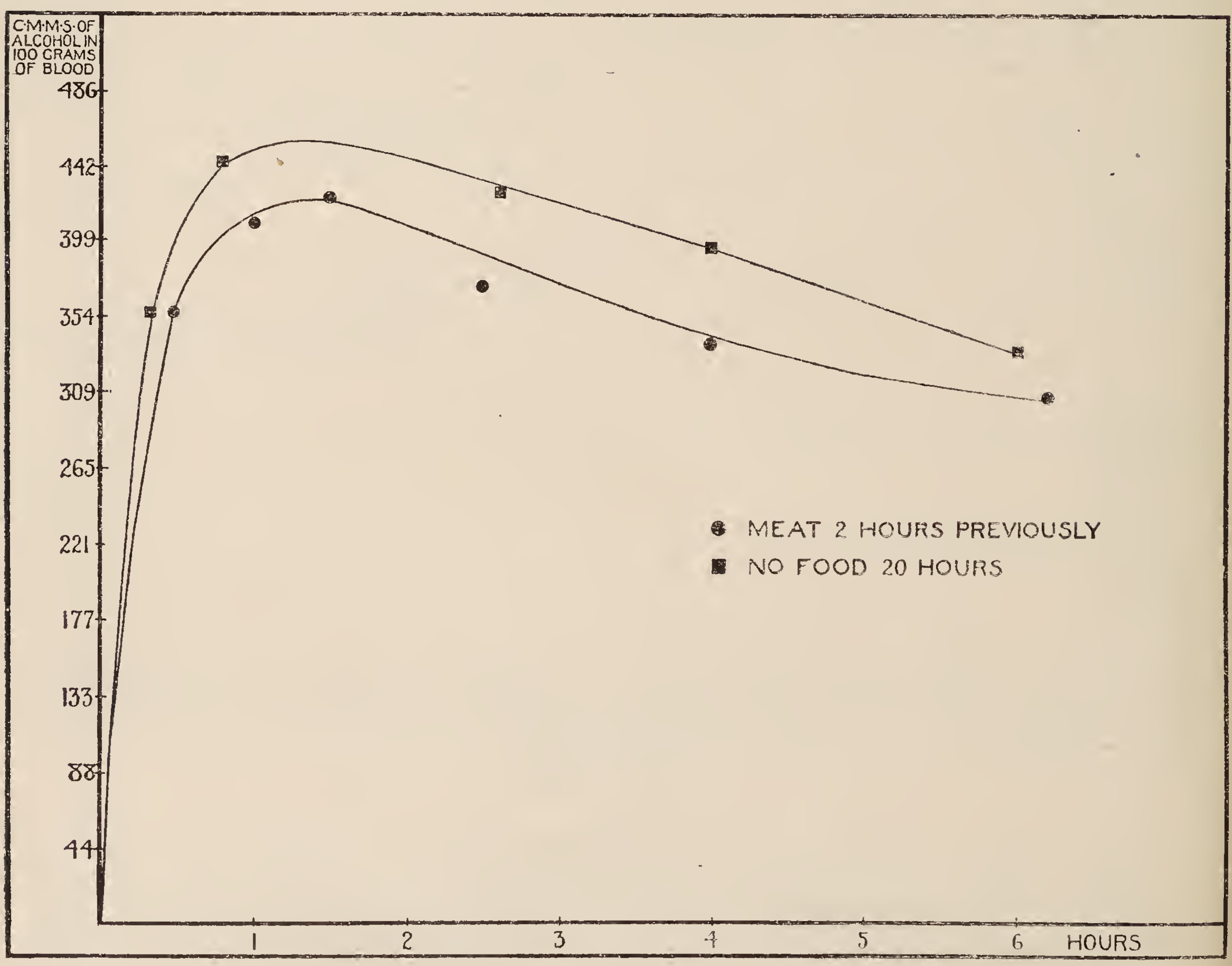

FIGURE XII.

when the stomach was empty. The presence of the meat depressed the rate of absorption and the maximum concentration of alcohol in the blood. The depressing effect is not so large as that possessed by milk.

Summary.

(1) Milk is the most effective food-stuff for delaying absorption of alcohol into the blood. It is almost equally effective whether mixed with the alcohol or drunk 2 hours before the alcohol. Its

action is quite independent of the dilution factor, although dilution with milk naturally acts in the same way as dilution with water.

(2) Cheese (war brand) had but little effect on the absorption of alcohol. The effect of meat was also small.

(3) Fat inhibits absorption of alcohol to some extent, and more especially that of stronger solutions (20 per cent.). The fat of milk is undoubtedly responsible for some of the inhibitory effect of milk, but possibly not all.

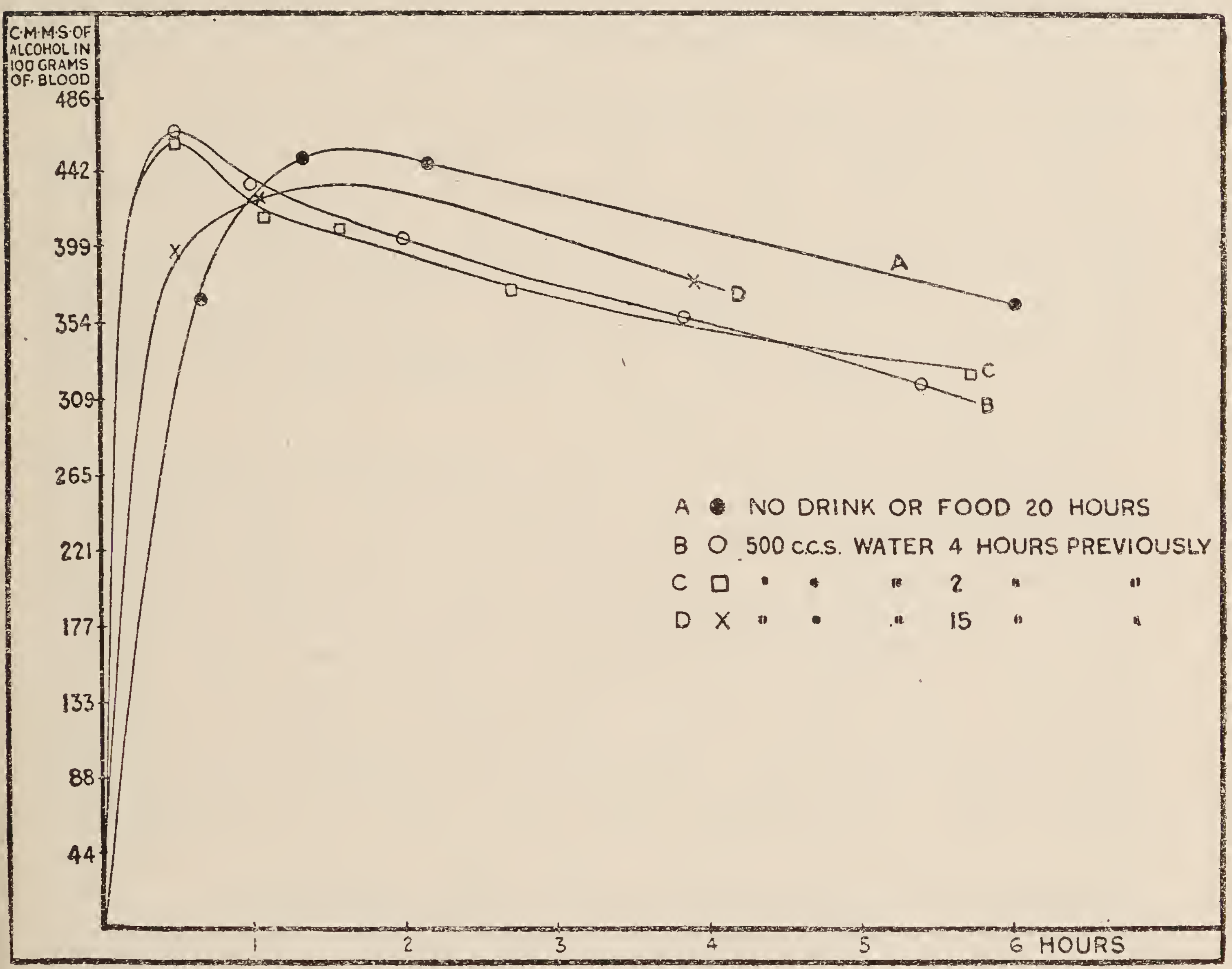

Figure XIII.

IX. The Effect of previously drinking Water on the Absorption of Alcohol.

It would be expected that the question of thirst as it involves absorption of alcohol from the alimentary canal would be simple, and that the more thirsty the animal the more rapid would be the absorption of alcohol. To some extent this is undoubtedly true, but complicating factors may be introduced into the experiments which do away with the possibility of attaching any importance to the generalization. In reality this is not surprising, for any specific absorptive action of the alimentary canal associated with thirst can only be brought about through a certain physiological condition of the intestine. If this condition could also be assured by the action of certain chemical substances on the mucous membrane of the alimentary canal, then rapid absorption would take place independently of thirst. If, further, it should happen that water is

a suitable substance for bringing about this specific condition, a more rapid absorption of alcohol in a dog after drinking water than in the same animal when thirsty might result. In these researches water has proved to be the best stimulus to absorption of all the substances investigated, so that we have the paradox of the most rapid absorption of alcoholic solutions taking place in animals the least thirsty. To place an alcoholic solution into the stomach immediately after drinking water would of course only result in the dilution of the alcohol, and the ordinary retardation of absorption associated with dilution. If, however, time is given to allow the water to be removed by absorption, say an interval of 2 hours, the alcohol will be very rapidly absorbed, because the water originally drunk has a certain stimulating action on the intestine.

This stimulating effect of water on alcohol absorption is well shown in Fig. XIII. In all experiments the water was withdrawn at 2 p.m. on the day prior to the experiment. In Curve C the dog drank 500 c.c. of water 2 hours before the administration of alcohol, and in Curve B the interval was 4 hours. In spite of this quenching of its thirst it will be seen that the alcohol was very rapidly absorbed, more rapidly indeed than when the dog got no water to drink (Curve A).

The same effect can be seen in Fig. III, described earlier, where alcoholic solutions were given at varying intervals. In such experiments the first drink of fluid brought about a more rapid absorption of subsequent drinks so long as the interval was not longer than 3 hours. After this time the effect of the previous fluid had apparently worn off, and the next solution of alcohol was more slowly absorbed. It would be well to point out here that the intervals mentioned only apply to these particular experiments, and that, whereas such results can undoubtedly be extended to man in a general way, corresponding data will have to be specifically obtained in man by similar experiments before the practical importance of the phenomenon can be fully appreciated.

To return to the theoretical side of the question, the stimulating effect of water on the absorption of alcohol from the alimentary canal may be of greater practical importance from a general physiological point of view than has been previously thought. The work of Pawlow[1] has made us familiar with the fact that water has a stimulating effect on the secretion of the gastric juice, probably in consequence of its power to liberate gastric secretin from the pyloric end of the stomach. In doing this it further augments the pancreatic and probably other secretions of the alimentary canal. Fowler and Hawk[2] have further shown that copious draughts of water increase the digestion and absorption of food-stuffs, and explained this by assuming that the increased secretions of digestive juices were responsible for a better reduction of the food-stuffs eaten to a form suitable for absorption. Since alcohol requires no digestion for absorption into the blood-stream, some other factor must be introduced to explain the stimulating effect of water, and it seems

[1] Pawlow and Thompson, *The Work of the Digestive Glands*, London; Griffin, 1910, 112.

[2] Fowler and Hawk, *J. Exper. M.*, N. Y., 1910, 12, 388.

probable that, in addition to its effect on the digestive juices, water has a specific stimulating effect on the cells of the intestinal mucous membrane responsible for absorption. The fact that the water effect continues even after 4 hours, suggests that its action may be due to a washing away from the walls of the alimentary canal of some substance normally inhibiting absorption. If, instead of water, milk be given before the alcohol, quite the opposite effect is produced and alcoholic absorption is greatly retarded. This is seen in Fig. XIV. In Curve C, 450 c.c. of milk was drunk 2 hours

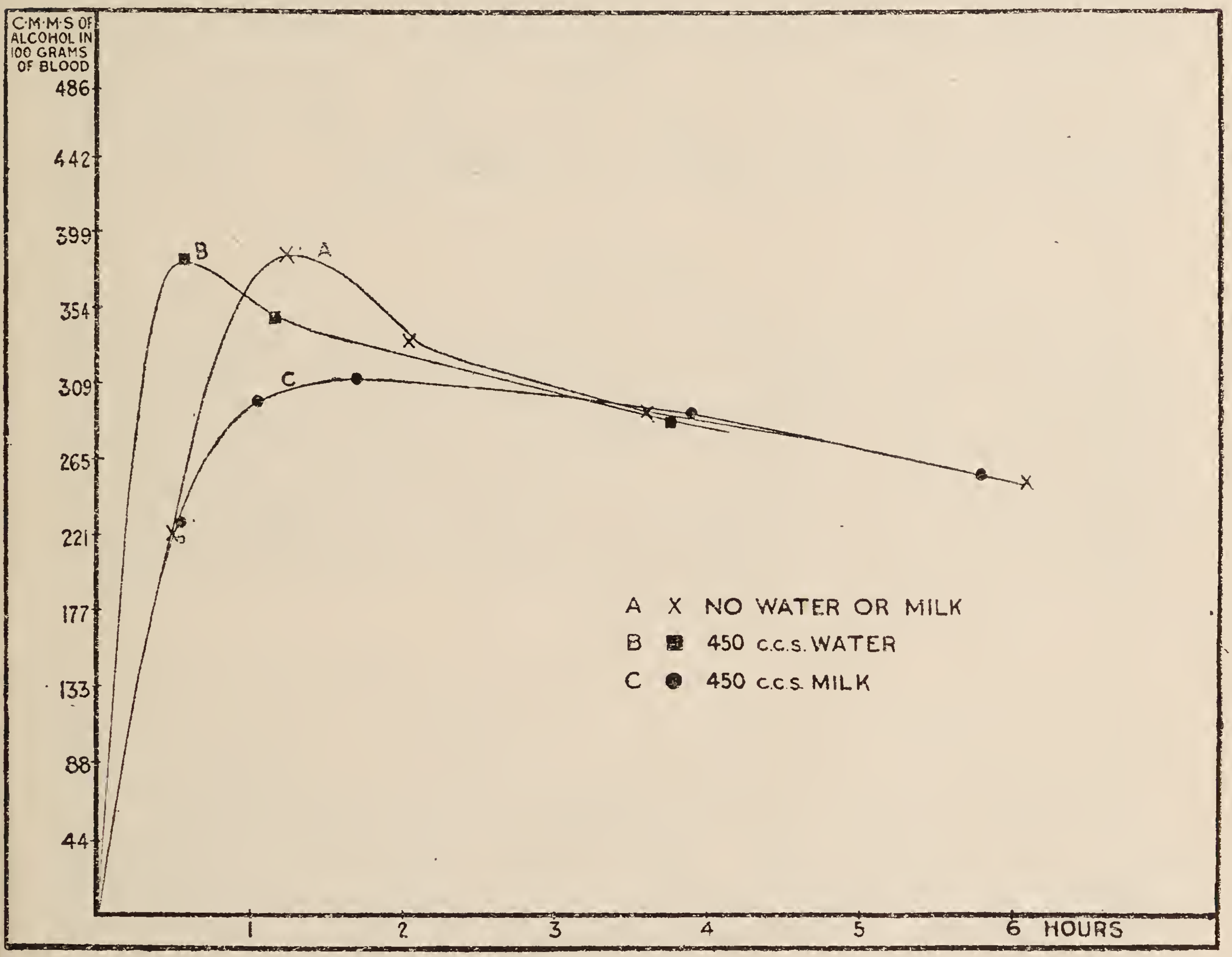

Figure XIV.

before the alcohol was taken. In Curve B, 450 c.c. of water was given, and in Curve A no food or fluid was allowed. The most rapid absorption is seen in Curve B, after water; the slowest in Curve C, after milk. It can be readily understood how different is the intoxication produced in the same animal by the same amount of alcohol under the different conditions.

These facts demonstrate how difficult it is to relate the absorption of alcohol to thirst, since the latter is completely dominated by certain conditions of the alimentary canal. If this can be eliminated by withholding fluid and food for many hours, then it is probable that the thirst factor may be of some importance, so that the more thirsty the animal the more rapid will be the absorption. Since, however, any animal would be thirsty to some degree after water has been withheld for the requisite number of hours, say 4 hours, the differences produced by different degrees of thirst would not be as pronounced as the differences already discussed.

The interpretation of these Curves in terms of intoxication will be discussed later.

Another point worthy of comment is the more rapid descent of Curves C and B (Fig. XIII), i.e. after the water has been drunk. This is probably due to the retention of the fluid previously drunk bringing about a greater dilution of the alcohol in the tissue fluids and blood. It appears as if the alcohol were rushed so rapidly into the blood that it had not time to get distributed in a normal way throughout the tissues of the body. After reaching a maximum the alcohol in the blood in Curves C and B is got rid of and distributed to other parts, bringing about an unnaturally rapid diminution. This is further exaggerated by the increased volume of fluid retained from the previously drunk water, so that the concentration of alcohol in the blood is alternately higher and lower than that existing when no water is drunk.

Summary.

The effect of thirst on the absorption of alcohol appears to be dominated by the condition of the alimentary canal. Water acts as the best stimulant to absorption so far discovered in these experiments, and a drink of water some hours before the alcohol causes a more rapid absorption of the latter. These results are in harmony with the previously observed fact that the fluid of a first drink of an alcoholic beverage can act as a stimulus to the absorption of the alcohol of a second drink.

X. The Effects of the Various Conditions on Intoxication.

It may be well to use the subject of intoxication as the peg upon which to hang and bring together the more salient facts described in the foregoing experiments. As I have pointed out in the beginning of this work, it is but a frail peg because of the impossibility in such experiments on dogs of measuring the degree of intoxication. It is true that there are certain definite signs of intoxication which might with great difficulty be classified in a certain order. Such signs, for instance, as scraping the toe-nails on the floor in walking, weakness in the hind legs as is evident on standing still, a rolling gait, stumbling, difficulty of getting on to feet after falling, and complete inability to walk, and collapse, are a series which act as a rough guide. They are, however, not sufficiently exact to bring into correlation with accurate alcohol estimations. Unfortunately also such symptoms usually appear in the first 2 hours of intoxication, and, after this period, except for considerable lethargy and general lack of interest in its surroundings, the dog may appear normal. This means that only the grosser kinds of inco-ordination are evident, and that, at a period when the animal must be considerably affected by the alcohol, which is at a high concentration in the blood, there is no reliable indication of the abnormality of the nervous system, much less can a true judgement be made of the intensity of the intoxication.

In dogs, therefore, the only symptoms of intoxication obvious are those mainly connected with balance and movement of the legs. In man inco-ordination is only a small part of the effect of alcohol, and yet it forms a more important part of the symptoms than in the dog. It has been pointed out that the hind legs of a dog are the first to show weakness, and that it is this which makes it more difficult for a dog to stand still than to walk when intoxicated. In walking, the weakness of the hind legs is compensated for by the front legs and the muscles of the other parts, and collapse prevented. Now in man the whole support of the body depends on the legs, and the base of the standing man is relatively much smaller than that of the dog. Consequently balance is a more difficult matter in an intoxicated man, and therefore unsteadiness is a more predominant feature in the complete picture. It can be readily understood how small is the part played by inco-ordination of the legs in the intoxication of dogs, and how difficult it is to apply such meagre results to man, especially as there is no means of judging all the other activities of the dog's brain and how they are influenced by intoxication. It is essential, therefore, to remember that the statements made in this section on intoxication demand confirmation at the hands of one who has reliable methods of estimating the intensity of intoxication. It is further necessary that these tests be directly applied to man, partly because it is easier, and more particularly because the question of alcoholic intoxication in man is the subject at issue.[1]

My justification for labouring this point is that I must confess to having been misled as to the real nature of the symptoms of intoxication and its relation to blood-alcohol by judging only of the dog's condition, and to have had my ideas altered by watching similar experiments in man which will be reported later. The rapid disappearance of inco-ordination in the early period of the experiments on dogs led me to believe that the recovery from intoxication was rapid. This I no longer believe, although, undoubtedly, improvement takes place immediately after the alcohol has reached a maximum in the blood.

I will now discuss the question as to how intoxication is influenced by various factors as it appeared in this experimental work.

(*a*) *The Amount of Alcohol drunk.*

It has already been seen in Fig. I that the amount of alcohol in the blood of a single animal is, other conditions being equal, proportional at its maximum to the amount drunk. This statement, however, does not appear to hold with any accuracy for small quantities of alcohol: in these experiments it does not hold when the alcohol consumed is 1·7 c.c. per kilo or less. With these smaller quantities of alcohol there is less in the blood than would be expected.

[1] Since these results were reported to the Scientific Committee of the Central Control Board (Liquor Traffic) work on these lines has been carried out by Dr. H. M. Vernon and Dr. Sullivan.

As the alcohol in the blood increases the symptoms of intoxication also increase. With dogs, however, a condition of affairs can be seen which is striking, but I rather doubt whether a similar change occurs in man. This is the relatively small increase in the alcohol of the blood which divides a dog slightly intoxicated from one helplessly intoxicated. In the case of the large brown dog, when the concentration of alcohol in the blood was 446 cm. per 100 grammes of blood the dog appeared slightly intoxicated, rolled a little on walking, could not stand steadily without support, and moved in a lethargic manner. When the concentration was raised to 468 cm. per 100 grammes the dog was profoundly intoxicated, could not get on to its feet even when helped, and for a period of time was in a collapsed state. The mild intoxication in this dog was produced by 50 c.c. of alcohol, and the intense intoxication by 55 c.c. The dramatic difference in the picture of intoxication produced by a small increase in alcohol is, I think, only striking because of the crudity of the indication of intoxication. Although the additional 5 c.c. of alcohol is the 'last straw', so to speak, the mechanism of co-ordination of walking is undoubtedly greatly influenced by the smaller dose, although the manifestation of such an influence is not so apparent because of the extraordinary strength of the entire mechanism. When it appears disarranged or affected as by the 50 c.c. of alcohol, it really is near the breaking-point. No doubt if there were means of measuring other actions of the nervous system of the dog, a gradual alteration in function as the alcohol in the blood increased would be found, and not the change to sudden collapse seen in the example discussed. In the experiments on men that I have performed I have seen no indication that a small increase in the alcohol of the blood synchronises with a sudden transformation of the intoxication symptoms. The whole picture, in fact, has appeared to me as a gradual development of symptoms with increasing alcohol.

A dog begins to show signs of intoxication when the alcohol of the blood reaches about 354 cm. per 100 grammes of blood. At this stage it will probably hit its hind toes against the floor on walking. Its movements will be slower and after a period of excitement its interest in external conditions will be less than usual. This only applies to the ascending portion of the curve. It has already been stated that the symptoms decline after the maximum of the alcohol in the blood has been reached. When the alcohol has declined again 354 cm. the dog will probably appear almost normal, and will certainly be less intoxicated than at the corresponding point on the ascent of the curve. The explanation of this may be along several lines.

(1) The nervous system is probably more affected by the sudden attack of the alcohol recorded by the upgrade course of the curve.

(2) The nervous system may re-learn to co-ordinate its activities after being under the alcoholic influence.

There is evidence that both these factors are involved in the course of a period of intoxication and both will be mentioned in due course.

(*b*) *The Rate of Absorption of Alcohol.*

It is difficult to differentiate between the effects of rate of absorption into the blood-stream and those due to its concentration, for a more rapid absorption is nearly always accompanied by a higher maximum. In Fig. XIII it will be seen that the curves of absorption after water (Curves B and C) are not only more rapid but their maximum point represents 464 cm. of alcohol in 100 grammes blood, while the corresponding number of Curve A, when the animal had had no food or water, is 453 cm. It was to be expected, therefore, that the animal in Curve B experiment would be more intoxicated than in Curve A. This was the case and the difference was great. It seemed possible that part, at least, of the increased symptoms might be due to a more rapid absorption of alcohol involving a more sudden attack on the nervous system. In order to get definite information on this point it is essential to compare a dog in two conditions, when the rate of absorption alters but the maximum point of concentration in both cases is the same. Such an instance is seen in Fig. VI, where a dog has taken stout, as in Curve B, and whisky diluted to the stout strength, as in Curve A. The rate of absorption of alcohol differs in these experiments, the maximum concentration in each case reaching 4·25 cm. per 100 grammes of blood. It seemed to me in this case and in similar experiments on another dog that the animals were undoubtedly more intoxicated after drinking the more rapidly absorbed dilute whisky. The period of more intense intoxication was but brief and diminished with the reduction of alcohol in the blood. In some cases of more rapid absorption, the rate of diminution of alcohol in the blood was also increased, so that the dog was intensely intoxicated for a short time, say 10–15 minutes, and then made a surprisingly rapid recovery (see Fig. XIII).

Previous work has all centred round the relation of intoxication to concentration of blood-alcohol, so that any other factor such as the one under discussion seemed worthy of mention. A crude kind of explanation of the increased inco-ordination of the grosser type produced by more rapid absorption of alcohol which might be suggested is that, when the attack of the alcohol on the nervous system is slow, the nerve-cells have the opportunity to re-arrange their interactions and call in additional nerve-cells to meet the new situation, but that, when the attack is more sudden, the cells are taken completely unaware and the system is suddenly knocked out of gear. That the nervous system can re-learn to co-ordinate under the influence of alcohol seems clear from the difference between a dog which has been held down on the table after receiving its requisite dose of alcohol until the time of maximum concentration, and the same dog which has been allowed to run about. In the latter case the dog re-learns as it runs, but, in the former, when released after being held down, it is often quite helpless for some minutes. After lying helpless it will pass through a period of experimental effort, endeavouring to rise, succeeding eventually only to fall down again and again, until finally an adequate mechanism of balance and co-ordination is called into play.

(c) *The Effect of Dilution.*

It has been seen that the effect of diluting alcoholic solutions (Fig. IV) is twofold: (1) the maximum concentration of alcohol in the blood is lowered, (2) the rate of absorption is depressed. It was further shown that the difference between the results obtained with strong and weak solutions became more marked the greater the quantity of alcohol drunk. In terms of intoxication, these results can be interpreted as follows: the greater the quantity of alcohol consumed, the greater is the difference in the intoxication produced by strong and weak solutions. Also, the more tolerant a man is of alcohol, that is, the higher the point the alcohol has to attain in the blood before desired symptoms of intoxication are produced, the more difficult will it be to produce these symptoms by dilute beverages. It was further seen that these results apply also to alcoholic beverages, e.g. whisky and stout, only that in this case another factor was apparently introduced, for the stout contained something which inhibited the absorption of alcohol. It was evident, for instance, that whisky diluted to stout strength was still more rapidly absorbed than stout. It ought to be more difficult to get drunk on stout containing 5·5 per cent. alcohol by volume than on a pure solution of alcohol of equal strength.

In Fig. V it was also seen that there was a considerable difference in the alcohol of the blood following the drinking of 5·5 per cent. and 3·9 per cent. stout. These facts have been discussed in a previous section; also the reason why the alcohol of the blood remains so much lower after drinking dilute beverages than after spirits has been discussed. It may be stated definitely that the differences in the intoxication produced by the various drinks are as characteristic and definite as are the blood-alcohol results. In the case of strong alcoholic solutions such as whisky, the symptoms come on more rapidly and are much more intense than with stout and other dilute solutions. No evidence, however, was obtained of there being any qualitative difference in the intoxicating symptoms produced by the different beverages.

In man, one factor bound up with the question of dilution must come into consideration which has been avoided purposely in these experiments. This factor is the ability to drink, during a specified period, an amount of fluid containing the quantity of alcohol requisite for intoxication. In normal times, with abundance of strong beer, this may not be of importance, but, at present, when Government ale containing only a small percentage of alcohol is the main drink, it must be somewhat difficult in the periods during which public-houses are open to drink the volume of fluid necessary to produce intoxication without bringing about vomiting, and incidently thereby avoiding intoxication. The consideration of this side of the question is, however, outside the scope of this paper. Here we have seen that, the greater the dilution of the fluid drunk, the lower is the alcohol concentration of the blood and the less rapid the absorption. The more diluted the beverage, therefore, the more alcohol has to be consumed to raise this substance in the blood to the requisite concentration for intoxication, and the more difficult is it to produce intoxication.

(*d*) *The Effects of Fluid and Food.*

We have seen that, on the whole, the presence of food in the alimentary canal inhibited the absorption of alcohol, so that a slower rate of accumulation of alcohol in the blood and a varying depression in the maximum concentration resulted when the stomach and intestines contained food. Substances varied considerably in their influence, so that whereas milk was the most active inhibitor, meat and cheese were the least. A hard fat like suet had an intermediate action between these substances, and, in addition, its effect was more obvious in connexion with strong than with weak alcoholic solutions.

One factor can be at once dealt with and eliminated. It might be thought that food-stuffs absorbed into the general circulation would play some part in aiding the defence of the body against alcohol. For instance, for many hours after a meal of fat, a considerable amount of this substance remains in the blood and other tissues, and the question arises as to whether this or other circulating food-material affects the course of intoxication independently of the alimentary canal. My observations lead me to believe that they do not, and that the interpretation of the curve of alcohol in the blood in terms of intoxication is the same in their absence as in their presence. This statement is made with some reserve and is subject to revision on further examination by more accurate methods. It is, of course, a most important point, for it might be possible to prevent intoxication or affect its development by food-stuffs in a manner other than by altering the absorption of alcohol from the intestine. If, for instance, the alcohol could be fixed in the circulating fluids and its access to nerve-cells prevented, a step of considerable practical importance would have been achieved. The symptoms of intoxication are strikingly depressed by milk, but I consider this depression can be satisfactorily explained by the altered curve of alcohol in the blood without assuming any action of the milk digest products present in the tissue fluids and body generally. If 6 or 8 hours be allowed between the consumption of the milk and the alcohol, the symptoms developed are usually as great as when no food has been taken, although digestive products must be circulating in the blood-stream. Therefore I am inclined to believe that, even in the food experiments, the curves of alcohol in the blood can be interpreted in terms of intoxication in the same way as when no food is taken.

Undoubtedly a part of the effect of food depends on the question of dilution of the alcohol in the alimentary canal, but only a part. For instance the inhibiting action of milk is evident after an interval of 3 hours, when it is certain that the fluid portion of the milk will have been absorbed. Probably the fat of milk is of importance in this respect, in view of the results described above with separated milk. However, I do not consider the fat can explain the whole result, which for the time being must remain incompletely accounted for.

In contrast with the effect of food on the absorption of alcohol we have seen the curious and unexpected results obtained with water. When alcohol is taken immediately after water the results

can be explained as simply those following dilution. When, however, a few hours' interval is allowed for the absorption of water, then alcohol is absorbed at a record rate, much faster indeed than in the same animal when thirsty. Fig. XIII demonstrates this fact and incidentally shows that the disappearance of alcohol from the blood is more rapid than in the control animal which has not received water. The condition of intoxication follows these curves. That is to say, 2 to 4 hours after drinking 500 c.c. of water the intoxication produced by the alcohol may be very intense, but an equally striking fact is the rapidity with which the intensity of intoxication diminishes. In such circumstances the dog may be more profoundly intoxicated 15 minutes after receiving the alcohol than the same dog, when no water has been drunk, 45 minutes after receiving the same amount of alcohol. On the other hand the recovery after water is much more rapid. No doubt the rapid recovery and the quicker descent of the alcohol curve after drinking abundant fluid can be associated with the retention of water in the body so that the total sum of body fluids is increased. In fact a condition of affairs arises such as has been met in the case of drinking a large volume of dilute 5 per cent. alcohol. In the above-described experiments 20 per cent. solutions of alcohol were taken by mouth. Thus we see that dilution of alcohol, and therefore an effect on intoxication, can be produced either directly in the intestine or indirectly in the body; the first by drinking dilute alcohol, the second by drinking alcohol some hours after water has been taken. The difference, however, between the effects on intoxication is that, whereas the first condition will alleviate the symptoms throughout, the second condition in the earlier periods of alcoholic absorption produces more intense intoxication than usual and the alleviation due to dilution follows this later. It is certainly most impressive to compare the relative intoxicating symptoms following a certain dose of alcohol in the same dog 2 hours after it has received respectively 500 c.c. of milk and 500 c.c. of water. In the first case the dog will probably show no sign of inco-ordination whatever, and in the second case will be quite incapable of standing or walking for some time.

(e) *The Relative Effects of Slow and Rapid Drinking.*

It has been stated that there is but little difference in the curves of alcohol absorption, whether a dog takes 250 c.c. of a 20 per cent. solution of alcohol at once or in four portions at 10 minutes intervals. In keeping with these facts the extent of intoxication was similar in both cases.

In other experiments (Fig. III) the intervals between the portions drunk were lengthened to 1, 2, and 3 hours. Naturally the shapes of the curves produced were altered, but, except in the case of the long interval of 3 hours, the maximum point of concentration was almost the same and the rate of accumulation of alcohol up to the maximum point identical, the rate becoming more rapid as the curves ascended. Whether the animal was given all the alcohol at once or in portions at intervals of 1 and 2 hours, therefore, the amount of intoxication at its worst was practically the

same, the only difference being that there was a delay in the development of symptoms corresponding to the delayed periods of drinking. When, however, the interval was extended to 3 hours, the maximum point attained was rather lower than in the foregoing experiments, and the rate of accumulation of alcohol in the body was relatively diminished after the second drink. The dog in this case was less intoxicated.

It may be well to point out that these results were obtained with a moderately strong solution of alcohol (i.e. 20 per cent.), and it is possible that different effects might be produced with more dilute drinks where the volume of fluid imbibed is greater, the time of absorption longer, and the dilution of alcohol in the blood owing to retained fluid more pronounced. Explanations of the facts have been offered in a previous part of this work, and here it only remains to say that, in order to alleviate symptoms of intoxication in dogs by drinking a definite quantity of alcohol in two or three portions rather than at once, the intervals must be long, probably a matter of 3 hours, and the longer the intervals the more obvious will be the difference in the condition of intoxication. Differences in intensity of intoxicating symptoms obtained by taking the same amount of alcohol in one or several drinks probably depend on the type of beverage drunk, and the intervals between the drinks.

Summary.

In this discussion of factors influencing intoxication, it is seen:

(1) That intoxication is related to the amount of alcohol in the blood and probably to the rate of accumulation in the blood.

(2) That dilute solutions of alcohol are less intoxicating than strong solutions containing the same amount of alcohol, the difference becoming more marked the greater the quantity of alcohol consumed and the greater the dilution.

(3) Food-stuffs inhibit intoxication in consequence of their action on the absorption of alcohol from the alimentary canal. The most effective food is milk, the action of which is dependent to some extent on its fat content.

(4) Water, after absorption, stimulates the absorption of alcohol, and thereby causes a rapid and intense intoxication from which recovery appears to be quicker than normal.

(5) Whisky is more intoxicating than stout, partly because of its greater concentration of alcohol, and partly because stout contains something which inhibits the absorption of alcohol to some extent.

(6) In order to obtain alleviation of symptoms of intoxication by splitting up an alcoholic beverage into two or three portions, the intervals between the drinks must be long, 3 or more hours, the time depending on the concentration of the fluid and the amount of alcohol contained therein. It is probable that the more dilute the beverage and the fewer the portions into which the drink is divided, the longer must be the interval between drinking in order to escape the maximum intoxicating symptoms.

XI. Alcohol as a Food.

Using the same method, that is to say, following up the alcohol content of the blood, some experiments were made to see if further insight could be obtained into the metabolic properties of alcohol. The results obtained in this investigation give no indication as to the fate of the alcohol as it disappears from the blood. On the other hand, they allow the subject of alcohol as a food to be approached from a different standpoint to that usually adopted, and, taken in conjunction with the researches of workers who have used other methods, they present a complementary picture which controls and in some cases extends present knowledge of this subject.

If we consider the large brown dog, it can be seen from the curves, e.g. Fig. II, that, after receiving 50 c.c. of alcohol, the blood was practically free from alcohol in 20 hours, i.e. at the rate of 2·5 c.c. per hour. The dog's weight was 13·5 kilograms, so that the rate of disappearance of alcohol was about 0·185 c.c. per kilogram weight per hour. If this were completely oxidized it would supply 1·04 calories. I do not know what the total loss of heat was in this dog during the experiment, but it would probably be something of the order of 2·5 calories per kilogram weight per hour. The energy supplied by alcoholic oxidation would therefore be about 41 per cent. of the whole loss. In the absence of figures giving the total loss of heat this figure is only a rough estimate. Völtz and Dietrich[1] have shown that 42 per cent. of the total energy of metabolism of resting dogs was supplied by alcoholic oxidation in a 10 hours' experiment, and 35 per cent. in a 15 hours' experiment. However, the energy supplied to the dog in the above experiment, i.e. 1·04 per kilogram per hour, is much higher than that calculated by Völtz and Dietrich. Probably some part of the discrepancy can be accounted for by the fact that the dogs used by Völtz and Dietrich were at rest, whereas my dogs were able to run about a room during the experiment.

Similar results have been obtained in experiments made to determine the effect of alcohol on the respiratory quotient. For instance, Higgins[2] has made use of Rosemann's[3] formula, and thereby estimated that the oxidation of alcohol supplies the human body with 28 per cent. up to 40 per cent. of the total energy lost during the experiments.

Rosemann's formula is

$$Oa = \frac{O(q - qa)}{q - 0{\cdot}667},$$

where Oa = oxygen consumed in burning alcohol.
O = total oxygen utilized.
q = respiratory quotient before the alcohol was given.
qa = „ „ after „ „ „
0·667 = „ „ for alcohol oxidation.

[1] Völtz u. Dietrich, *Biochem. Ztschr.*, Berl., 1915, 68, 118.
[2] Higgins, *J. Pharmakol. & Exper. Therap.*, Balt., 1917, 9, 441.
[3] Rosemann, *Oppenheimers Handbuch d. Biochemie*, 1911, 4 (1), 423.

Using this formula the amount of oxygen used up in the oxidation of alcohol has been calculated, and this allows the percentage of the total energy supplied by alcoholic oxidation to be determined. Criticism of Rosemann's formula will be made later.

It has been previously pointed out in this paper that the rate of alcohol combustion is independent of the amount drunk, so that, whether the animal received a great or a small quantity of alcohol, the rate of oxidation remained approximately the same, and therefore the amount of energy in unit time supplied to the metabolism remained unchanged. Using the respiratory quotient method Higgins has come to a similar result. He found that the drop in the respiratory quotient produced by alcohol in resting men was the same whether 30 c.c. or 45 c.c. was drunk, so that the amount of oxygen used up by the alcohol in unit time was the same in spite of the varying amounts of alcohol imbibed. Now this conclusion is an important one, and places alcohol in a different category from other non-nitrogenous food-stuffs, for in these cases, at least with fats and carbohydrates, the evidence indicates that the effect on the metabolism distinctly varies with the amount consumed. The following figures[1] obtained by Gephart and Du Bois show the effect on the respiratory quotient of giving varying quantities of glucose to man:

Hours after food	1	2	3	4
100 grammes glucose	0·91	0·89	0·88	0·90
200 " "	—	0·95	0·93	0·95

It is evident that more glucose is being oxidized when the large quantity is eaten, for the respiratory quotient rises considerably higher in the case of the 200 grammes experiment. It was further observed that 100 grammes of glucose caused an average increase of 9 per cent. in the heat production, and 200 grammes an increase of 12·5 per cent. during the 3 to 6 hours after ingestion. Fisher and Wishart,[2] working in Lusk's laboratory, found that the height of metabolism was about the same whether 50 or 75 grammes of glucose were taken by dogs, only in the latter case the effect was prolonged. Their curves, however. show that carbohydrate affected the respiratory quotient to a greater degree when the larger quantity was taken, as was seen above in the Gephart and Du Bois[3] results.

In the case of fat also, previous experimental work has shown that the metabolism is quantitatively affected by varying quantities. Forssner[4] has obtained the following results after giving varying quantities of olive oil to a man on a diet of sufficient caloric value (3,380 calories), but deficient in carbohydrate (160 grammes).

	Total acetone bodies	β-oxybutyric acid
No olive oil	5·11 grammes	3·69 grammes
40 grammes olive oil	9·16	7·22
60 " "	9·96	8·08
80 " "	11·80	9·52

[1] The following examples were taken from G. Lusk's book, *Science of Nutrition* (Saunders), 1917.
[2] Fisher and Wishart, *J. Biol. Chem.*, N.Y., 1912, 13, 49.
[3] Gephart and Du Bois, *Arch. Int. Med.*, Chicago, 1915, 15, 835.
[4] Forssner, *Skandin. Arch. f. Physiol.*, Leipz., 1910, 23, 1915.

These amounts were excreted between 11.0 p.m. and 10.0 a.m. of the following day. No doubt the increase in fat combustion would be more obvious with increase in amount ingested if a sufficiency of carbohydrate had been present.

Again Magnus-Levy[1] obtained an increase of 10 per cent. in metabolism above the original basal level on giving a dog 140 grammes of bacon fat. When 320 grammes of the fat were eaten there was an increase of 19 per cent. in the metabolism between the 3rd and 6th hours. These results obtained with carbohydrates and fats indicate that there is a quantitative relation between the amount eaten and the effect on the metabolism, and we have further seen that no such relation as this holds in the case of alcohol, where the amount oxidized is apparently independent of the amount imbibed.

Rosemann's[2] formula given above was designed to afford information as to the amount of oxygen used up in the oxidation of alcohol over any specific time. From this it can be calculated at what rate the alcohol is being oxidized. The development of the formula depends on two points, (1) that as the result of drinking alcohol there is no increase in the total oxygen intake; (2) that the respiratory quotient for substances other than alcohol before and after its entry into the blood-stream remains the same: that is to say, the alcohol replaces carbohydrates and fats in the same proportion as was being oxidized prior to the alcohol being drunk. Now the first of these points is a fact, and the second is an assumption which seems to me to be incorrect. In Higgins's[3] respiratory quotient experiments it was shown that the higher the respiratory quotient the greater was the fall produced by alcohol.

The following table is a summary of results obtained in his respiratory quotient experiments, together with the amounts of alcohol oxidized per hour calculated on the basis of Rosemann's formula:

Average Respiratory Quotients following the giving of 30 c.c. Alcohol.

R. Q. before alcohol	R. Q. after alcohol	Drop due to alcohol	Calculation of percentage of total O_2 consumption caused by alcohol (Rosemann's formula)	Calculated amount of alcohol burned per hour
0·90	0·805	0·095	40 %	4·91 c.c.
0·85	0·795	0·055	28 %	3·68
0·80	0·775	0·025	20 %	2·75

We see that, according to the above calculations, the rate of combustion of alcohol was greater when the initial respiratory quotient was high, i. e. when the combustion of carbohydrate was predominant, than when low, at which time a greater proportion of fat was being oxidized.

[1] Magnus-Levy, *Arch. f. d. ges. Physiol.*, 1894, **55**, 1.
[2] Rosemann, loc. cit.
[3] Higgins, loc. cit.

In the type of experiment described in this work, where the alcohol in the blood is directly calculated, it is obviously possible to test the accuracy of the above deductions. Fig. XV represents the disappearance of alcohol from the blood in a dog, which received 50 c.c. of alcohol in a 20 per cent. solution after it had eaten A. meat, B. fat, C. bread and milk. It is certain that the initial respiratory quotients must have been very dissimilar as the result of eating these different types of food-stuff. With fat the quotient would be low, with bread and milk higher and more approximate to the figure for carbohydrate. It will be seen that the rate of disappearance of alcohol from the blood, and, probably therefore, its rate of oxidation in the body, is practically the same under these

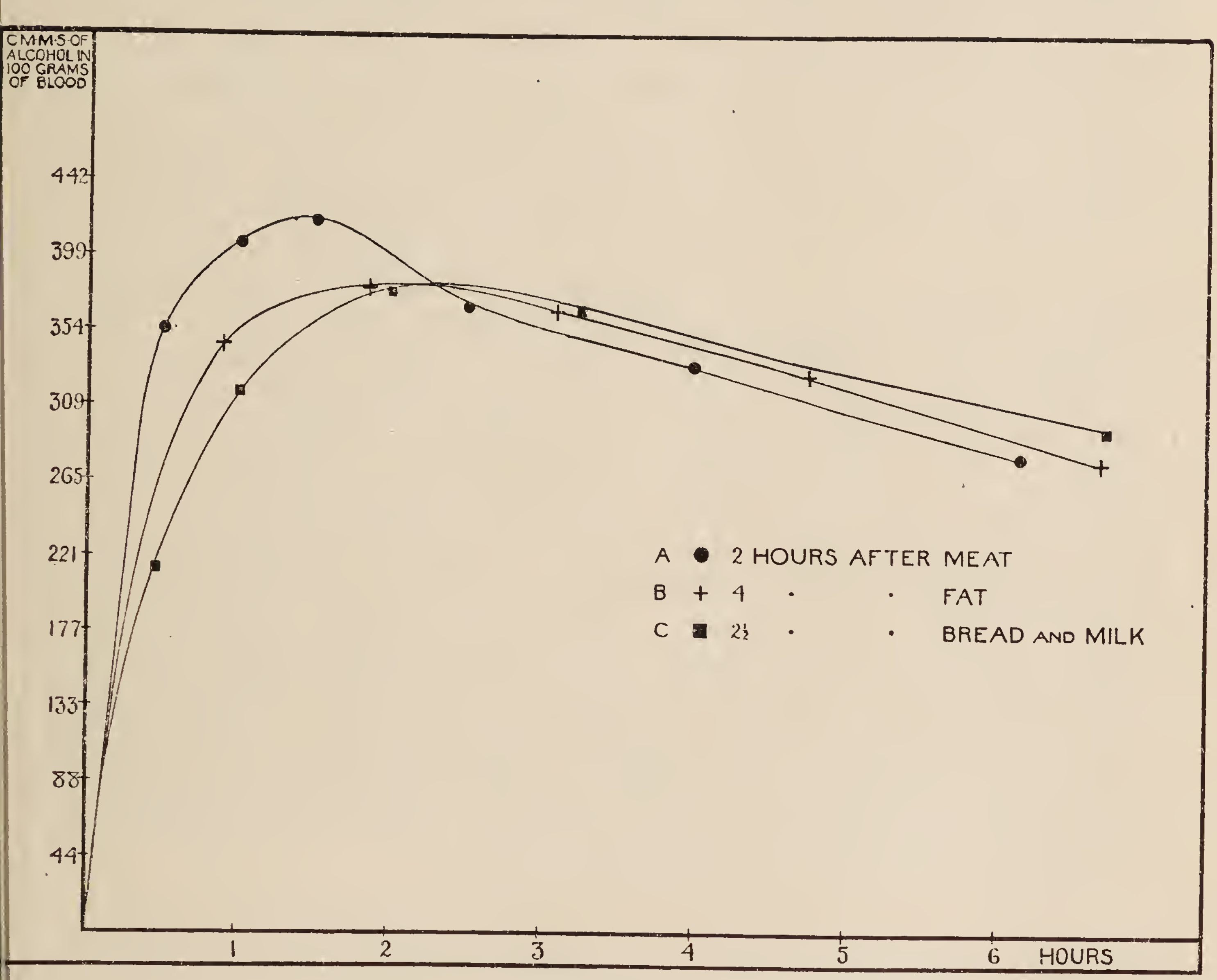

Figure XV.

various conditions. There is no evidence that the rate of combustion of alcohol, when carbohydrate is playing a predominant part, is any higher than when fat is of greater importance. If this is true, then it can no longer be held that the combustion of carbohydrate and fat proceeds at the same relative rate before and after alcohol. An alternative supposition that, when the respiratory quotient is high, more carbohydrate is replaced by alcohol, and when low, a relatively smaller quantity, is more likely to be true in face of the above facts. To what extent the deductions made on the basis of Rosemann's formula are incorrect I do not know. Working under constant conditions without much variation in diet and alcohol consumption, the error may not be of much importance. The point seemed to be of sufficient interest

to merit discussion here. The other basis of Rosemann's formula, viz. that alcohol does not increase the total oxygen consumption, is based on definite experimental evidence adequately confirmed in the experiments of Higgins. It is a point of some importance and shows that, having no specific dynamic action, alcohol must be considered from still another point of view as on a different basis from other food-stuffs. For whatever may be the real explanation of the specific dynamic action of food-stuffs, the stimulating action of proteins, fats, and carbohydrates on the general metabolism is undoubted. Alcohol as a food-stuff, on the other hand, simply replaces certain quantities of carbohydrate and fat, and has no stimulating effect on the metabolic processes of the body and, indeed, does not add to the brightness of the flame. In contrast to the fact that alcohol, in its food effect, does not increase the total heat produced in the body, it is certain that it does increase the heat loss by causing vaso-dilatation of the skin vessels. The result must therefore be a fall in body temperature, which may not be large or important if the animal is receiving a sufficiency of proteins, fats, and carbohydrates as food, but may be serious when, owing to the lack of food, the level of combustion is low. In starvation, for instance, and even more so in starvation combined with exposure, the taking of alcohol, quite apart from its deleterious actions on the central nervous system and neuromuscular mechanism generally, the effect of which is to make the person drowsy and lethargic and thereby to diminish the heat production, may have serious results in consequence of this antipyretic effect. In such cases alcohol does not increase the amount of energy available for immediate use, while it increases the heat loss by causing vaso-dilatation of the skin vessels, an action which is the basis of the improved feeling of warmth and well-being following its use. Were it the case that death due to starvation and exposure resulted from a lack of protein, fat, and carbohydrate stores in the body, alcohol might be more useful in such conditions. Since this is not the case, the benefits that it produces are probably more than balanced by its baneful effects.

Summary.

While it is undoubted that alcohol can supply a large part of the total energy lost by the body (30 per cent. to 40 per cent.), it appears to be different from the other non-nitrogenous food-stuffs in several ways:

(1) Its rate of combustion is independent of the amount circulating in the blood within fairly wide limits.

(2) It has no specific dynamic action, but simply replaces other food-stuffs without stimulating the total combustion processes.

(3) Its rate of combustion is apparently independent of the types of other food-stuffs being metabolized.

XII. The Effect of Exercise on the Rate of Combustion of Alcohol.

The conclusions to be drawn from the experimental results of this work as regards the rate of combustion of alcohol in the body, are in so close agreement with the results obtained by other workers using the methods of calorimetry and respiratory quotients, that it is justifiable to assume that the rate of disappearance of alcohol from the blood is a direct measure of its rate of combustion. The advantage of this method is that the rate of combustion of the alcohol can be determined directly at any moment. With calorimetry and respiratory quotient experiments the interpretation of the results is often indirect, and dependent on hypotheses which in some cases are probably not sound. It may therefore happen that, in these indirect methods of experimentation on alcohol metabolism, points may be missed which are revealed by the direct determination method. The ideal conditions of experimentation would be to supplement the calorimetry methods with estimations of alcohol in the blood, and thereby obtain some direct indication of alcoholic changes at particular moments.

The work of Atwater and Benedict[1] has made it apparent that alcohol can replace fats and carbohydrates isodynamically either in the active or resting states. It is true that they introduce the pharmaco-dynamic or drug-action of alcohol in addition to its nutritive action, in the endeavour to harmonize the results obtained by themselves and other workers of experiments, which were undertaken to demonstrate the sparing effect of alcohol on protein metabolism. This point is not emphasized in the portion of their researches dealing with muscular work. It is probable that this pharmaco-dynamic action was of no consequence in their work experiments because of the small quantities of alcohol used (72 c.c. per diem). After reading Atwater and Benedict's work, the impression is formed that alcohol can be considered on the same basis as carbohydrates and fats as a source of energy in every sense of the word, and the point is of such importance that I think it necessary to lay stress on the following results obtained in experiments showing the effect of exercise on the rate of combustion of alcohol. If Atwater and Benedict's conclusions are true, during mechanical work the rate of combustion of alcohol must increase in the same ratio as the total increase in metabolism. That is to say, alcohol must provide the same percentage of energy during muscular work as at rest. In these experiments, therefore, it would be expected that the rate of disappearance of alcohol from the blood would be greatly increased during exercise.

In the resting experiments the animals were confined for the period of the experiment (about 6 hours) to a small cage, and in the exercise experiments the same animals ran about in the open, and were generally encouraged to do this as vigorously as they were able during the period. In some cases, and more particularly when larger quantities of alcohol were given, the dogs ran behind a bicycle, care being taken not to run them to exhaustion, which is brought on easily in animals under the influence of alcohol. With

[1] Atwater and Benedict, loc. cit.

smaller quantities of alcohol the natural vigour of the dogs was but little affected, and it was unnecessary to use much artificial stimulus to promote activity.

The earlier experiments performed indicated that alcohol was slowly consumed in a dog either active or resting, and that there was but little difference in the rates of oxidation in the two conditions. This point is seen in Fig. XVI, Curves A and B, where

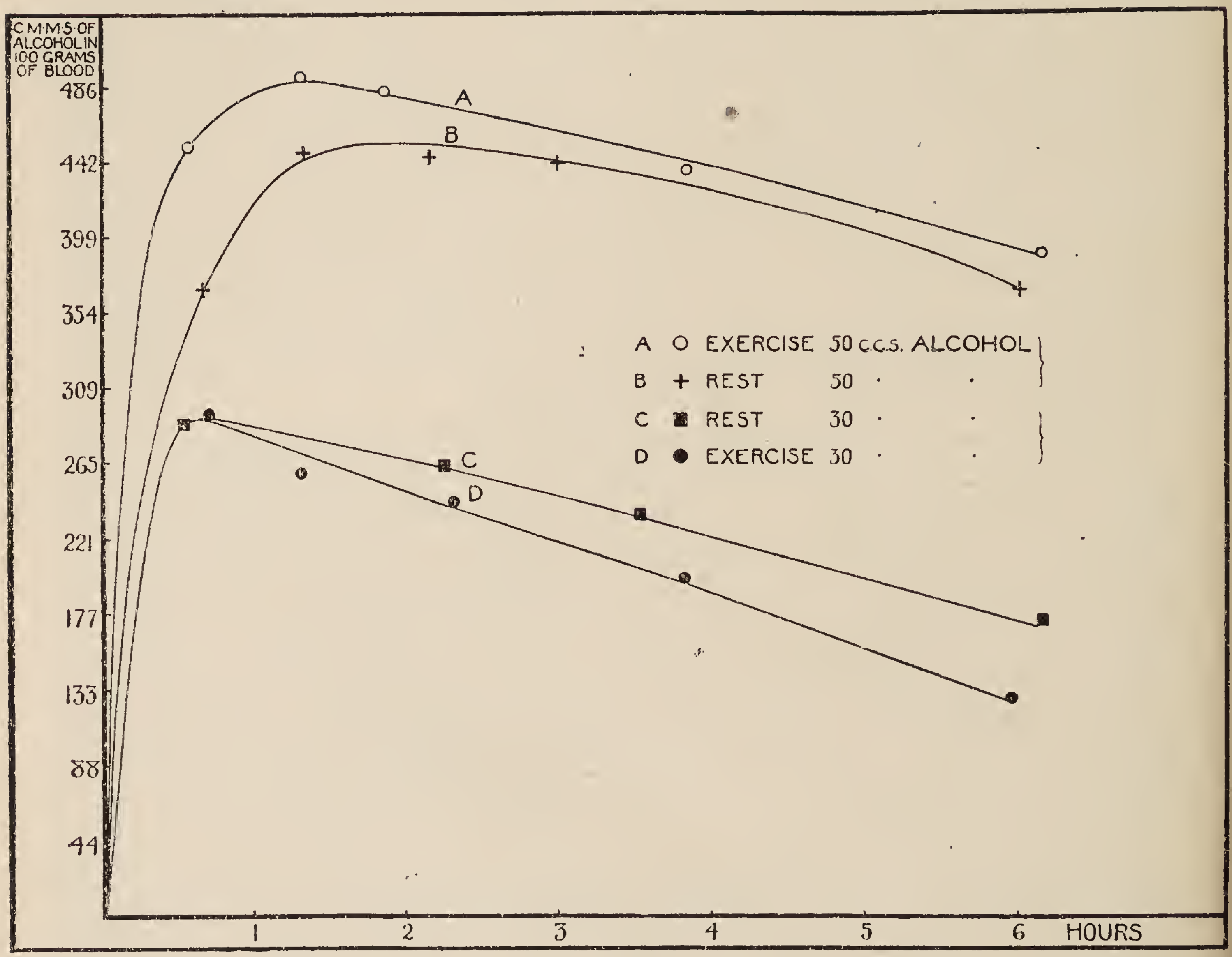

FIGURE XVI.

the rates of disappearance in the two conditions are practically identical. In these experiments the dog received 4·1 c.c. of alcohol per kilogram weight. This and similar results obtained with other dogs spoke against the deductions from Atwater and Benedict's experiments, for, if exercise does not increase the rate of combustion of alcohol, then the substance cannot be considered on an isodynamic basis with carbohydrate and fat, the combustion of both of which is increased by an augmentation of physiological activity. It was, however, thought desirable to diminish the amount of alcohol given. This was done, and Curves C and D were obtained when the dog was given 30 c.c. of alcohol or 2·5 c.c. per kilogram weight. In these curves it will be seen that exercise has increased the rate of disappearance of alcohol from the blood, and, in fact, at the end of 6 hours there is approximately 4 c.c. less alcohol in the body of the dog after exercise, assuming that the concentration of alcohol in the blood is a measure of total alcohol in the body.

This result is even more pronounced in Fig. XVII, where 20 c.c. of alcohol were given in a 20 per cent. solution, or 2·0 c.c. per kilogram weight, to another dog. The exercise Curve C descends more rapidly than the rest Curve A, and roughly speaking the dog in the resting state at the end of 6 hours has about 6 c.c. more alcohol left in its body than after taking exercise. Curve B represents another resting experiment under the same condition as A. In the experiment of Curve D, the animal ran about except for a rest of 1 hour after the alcohol had been injected 1½ hours. Towards the end of the experiment also there was another rest interval. Both of these periods of rest are indicated in the resulting curve by the diminished rate of disappearance of alcohol from the blood. The results obtained with the lower concentration of

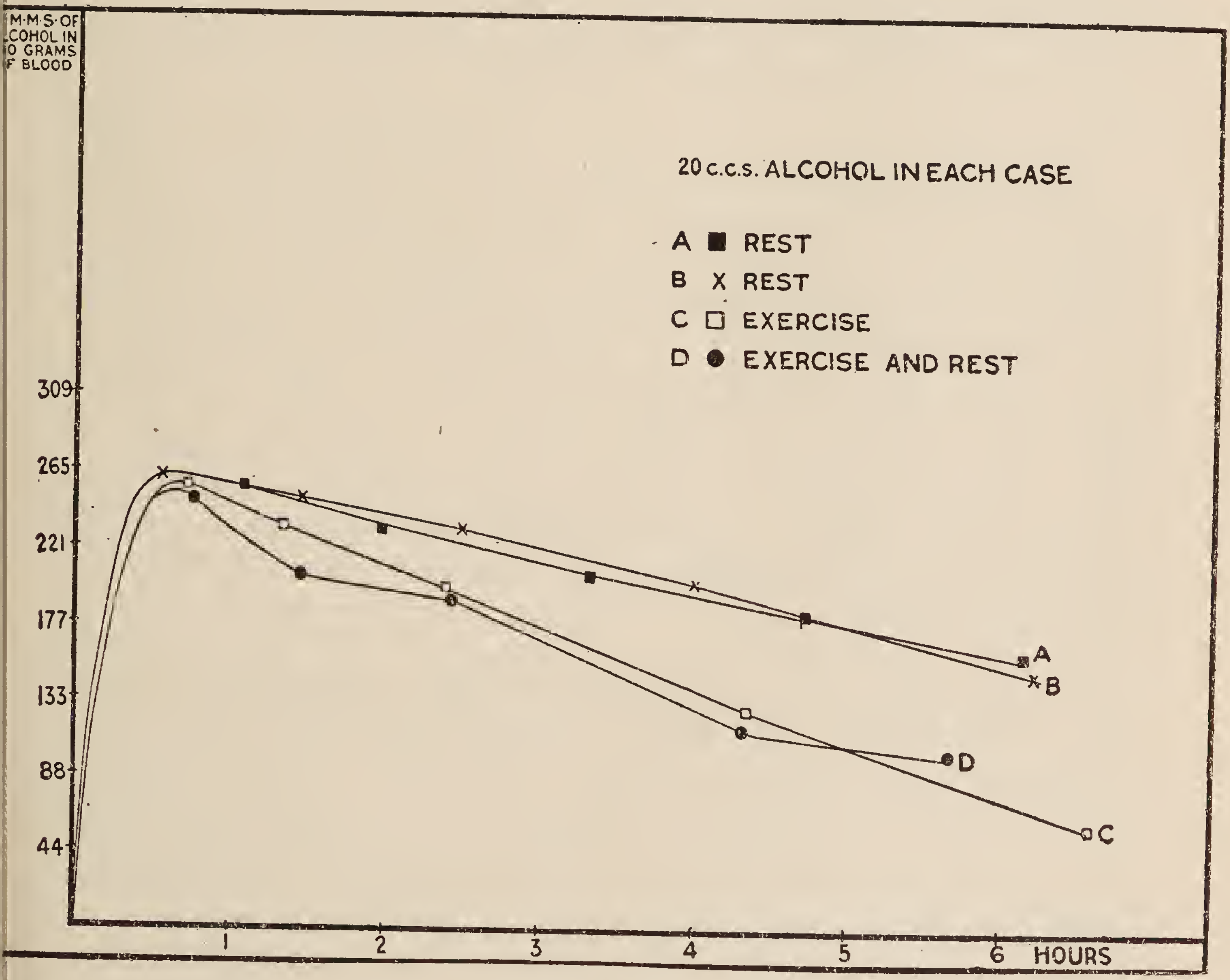

FIGURE XVII.

alcohol are those where the conditions more closely approximate to the conditions of Atwater and Benedict, who worked with quantities of alcohol which could have only produced low concentration in the blood. In these curves there is distinct evidence that the rate of combustion of alcohol is increased with an increase of bodily activity. With the curves of higher concentration there is no evidence that the rate of combustion of alcohol is altered in any degree by muscular work. Why is there this difference? It may be, of course, that with the smaller concentrations of alcohol in the blood, the dogs were capable of doing much more work than when under greater toxic influence of the drug. The dogs were certainly

much more active. At the same time it must be pointed out that even with the larger doses of alcohol, although easily fatigued, the dogs did a considerable amount of running about, and probably covered 8 to 10 miles in the experimental period. It may well be, however, that the increased activity with the lower concentration accentuated the difference in the rate of oxidation, although it is difficult to understand why there should be no increase with muscular activity at the higher concentrations.

One other factor must be taken into consideration, although on its importance I am not inclined to place much value. The results of Atwater and Benedict show that of the alcohol imbibed only a very small proportion (about 2 per cent.) escaped oxidation, and was excreted unchanged either in the breath or urine. Against these results must be mentioned the work of Völtz and Baudrexel,[1] on dogs specifically designed to determine how much alcohol escaped oxidation under varying conditions. This latter work is not in harmony with that of Atwater and Benedict, for they came to the conclusion that as much as 10 to 12 per cent. of the alcohol drunk could be excreted unchanged in the expired air and urine, and one of the conditions which increased the excreted alcohol most effectively was exercise. The total respiratory ventilation was, under such conditions, largely increased. It is possible, therefore, that some part of the augmented rate of disappearance of alcohol from the blood during the exercise experiments may be due to the greater respiratory exchange and the excretion of alcohol through the lungs. It is further possible that the results of Völtz and Baudrexel may partially explain the inharmonious nature of the curves obtained when greater and less quantities of alcohol were given. With the smaller concentrations the dogs not only ran about more vigorously but also panted to a greater degree, and therefore increased the opportunity for the respiratory excretion of alcohol. Völtz and Baudrexel also showed that larger percentages of alcohol were excreted when more alcohol was given, and therefore it would be expected that the lung excretion factor, if of any importance, would at least be obvious in the exercise experiments of higher alcoholic concentrations (Fig. XVI, Curves A and B). With greater concentration of alcohol in the blood, the diffusion across the lung capillary-walls and lung endothelium ought to be more prominent. However, it is just in these experiments (involving higher concentrations of alcohol in the blood) that there is no difference in the angle of descent of the resting and exercise curves, and no indication of increased alcohol excretion is perceptible. Even if their results are accepted, they could not explain the difference of the amount of alcohol in the blood seen in Fig. XVII curves. Here, at the end of the experiments, there was approximately 6 to 7 c.c. more alcohol in the resting than in the active body. Six c.c. out of a total of 20 c.c. alcohol imbibed is more than could be accounted for by Völtz and Baudrexel's results, where the percentage of alcohol excreted in the breath and urine in no case exceeds 12 per cent. of the total. I conclude, therefore, that alcohol combustion is increased with exercise when the alcohol concentration in the

[1] Völtz u. Baudrexel, *Arch. f. d. ges. Physiol.*, 1911, **142**, 47.

blood is low. When, however, the concentration is increased, the energy obtained from this source in unit time is limited to that of the resting condition, probably in consequence of the toxic action of the alcohol on the cells of the body. The larger doses of alcohol not only diminish the total mechanical work capable of being performed, but also prevent the body from obtaining any increase of energy required for this work from the combustion of the narcotic substance.

In keeping with this suggestion is the rapid fatigue which develops in the more intoxicated dogs, this fatigue being quite apart from the evident sleepiness and laziness associated with alcohol. Since fatigue is largely dependent upon the production of substances such, for instance, as lactic acid, whose presence is notoriously indicative of deficient oxidation, it suggests that a high concentration of alcohol in the body not only limits its own oxidation but also limits the oxidation of other sources of energy, and so brings about the subsequent accumulation of intermediate oxidation products and rapid fatigue.

In the experiments of Fig. XVII, where the dog received 2 c.c. alcohol per kilogram, the energy supplied in the combustion of the alcohol in the resting period is 0·74 calories per kilogram weight per hour. In the exercise experiment with the same dog the energy supplied in this way increased to 1·27 calories per kilogram weight per hour. Unfortunately no figures of the total energy lost in the resting and exercise experiments are available, so that it is impossible to say whether the increase due to exercise is proportional to the increased heat-loss. If the increase in alcohol oxidation is proportional to the total increased energy changes, then it is clear that, in the lower concentrations of alcohol used, the alcohol is being burnt up during exercise isodynamically with the other combustible food-stuffs.

In this connexion, experimental work by Durig[1] on the rate of alcohol combustion is of interest. This worker examined the effect of alcohol on the respiratory quotient of men during climbing. Normally, without alcohol, the effect of climbing a mountain was to cause a decline in the respiratory quotient. When, however, alcohol had been taken before the ascent (1 litre of beer containing 35 grammes of alcohol) the respiratory quotient remained constant or increased. The effect of taking alcohol in a resting condition is to produce a descent in the respiratory quotient (R. Q. for alcohol is 0·667), so that, in the mechanical effort of climbing, the energy was not obtained at the expense of a proportionate combustion of alcohol, but was supplied to a greater degree by carbohydrate oxidation. It appeared that the rate of combustion of alcohol was increased by mechanical work, but under the conditions of Durig's experiment it did not supply the same proportion of energy to the body in the resting and active states. It is necessary to point out that the amount of alcohol in Durig's experiments was smaller than in Atwater and Benedict's experiments (35 grammes against 72 c.c.), and much smaller proportionally than in my own. The alcohol was taken at breakfast by Durig, but

[1] Durig, *Arch. f. d. ges. Physiol.*, 1906, **113**, 213, 341.

at intervals during the course of the day in Atwater and Benedict's experiments.

Whether alcohol can supply the energy for muscular contraction has never, to my knowledge, been decided. Atwater and Benedict on this particular point write: 'That alcohol contributes its share of energy for muscular work is a natural hypothesis which is very probable but not absolutely proven. The hypothesis that the energy of alcohol is not so used is not called for as an explanation of any fact observed in these experiments.' We see, however, from the above-described experiments (with higher concentrations of alcohol), and from Durig's work, that there is evidence that alcohol does not always contribute its share of energy for muscular work, or, at least, does not contribute the same proportion of energy in the resting and active states. Although these results do not prove that alcohol is not a source of energy for muscular contraction, they certainly seem to me to suggest strongly that this is the case. Alcohol combustion does indeed supply heat to the body, but even if the possibility of its providing some of the energy for the contraction of muscles is accepted, it obviously cannot be considered in the same category as other food-stuffs, even when present in the body as in Durig's experiments in minimal quantities, on which occasions its toxic or pharmacodynamic action must have been negligible.

Summary.

The results of these experiments indicate that, whereas alcohol, when present in low concentrations in the body, undergoes combustion at a more rapid rate during exercise than at rest, and therefore supplies a greater amount of energy to the active organism, at higher concentrations it is only oxidized at the same rate in the resting and active animal. In other words, the greater the toxic action of alcohol the more limited is the increase in its rate of combustion by exercise, and the closer do the rates of combustion of alcohol in the active and resting states approximate. Alcohol at high concentrations seems not only to have this self-limiting action on its own oxidative process, but, if fatigue is a true indication of diminished or partial oxidation, to extend its baneful and detrimental influence to the limitation of the oxidation of other combustible material.